Wilson HTM
EQUITIES RESEARCH

06 October 2015

ONCOSIL MEDICAL (OSL)

BUY | HOLD | SELL

Initiating coverage

A great time to be developing new brachytherapy devices

We initiate coverage on Oncosil Medical with a SPECULATIVE BUY rating and a risked price target of 35 cps (un-risked 100 cps). A new initiative at the US Food and Drug Administration could potentially ease the path to initial approvals for medical devices in areas as desperate as pancreatic cancer. Oncosil's medical device fits the profile: a radioactive implant designed to ablate aggressive, primary pancreatic tumours, in a single procedure with good safety. Nothing on the market does that well enough and the prognosis for people diagnosed with this disease is poor. We assess early clinical interest in Oncosil, which is designing a pivotal trial in the US. A modest launch in Europe is planned for 2016, but the explosive catalyst for this stock will be the FDA's review and potential approval of Oncosil's proposed pivotal US trial plan, later this year.

12-mth target price (AUD)	**$0.35**
Share price @ 01-Oct-15 (AUD)	$0.17
Forecast 12-mth capital return	104.6%
Forecast 12-mth dividend yield	0.0%
12-mth total expected return	**104.6%**
Market cap	$61m
Enterprise value	$42m
Shares on issue	356m
Sold short	0.2
ASX 300 weight	n/a
Median turnover/day	$0.1m

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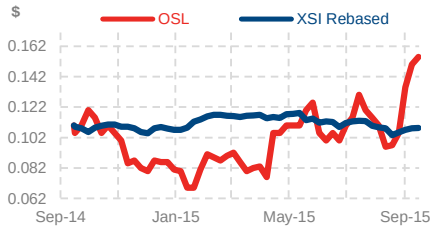
Key points

Introducing Oncosil Medical – this Australian medical device company is responding to one of the most pressing problems in solid tumour oncology today – how to rapidly "de-escalate" aggressive pancreatic cancers. Current radiological methods are inadequate, which is why they have been relegated, over the past decade or so, to a largely palliative role. Oncosil has developed an implantable, radioactive device which can deliver a large, potentially decisive dose of radiation in one sitting, to shrink tumours with good safety. The company is readying a modest European launch and a pivotal Phase III trial in the US next year. We assess peak sales in the order of A$350-400m for the treatment of locally advanced and metastatic pancreatic cancer.

The drive towards Level 1 clinical evidence – Oncosil's current data comprises four Phase II trials conducted in small numbers of patients. Its development plan is adequate to generate higher level evidence, on which marketing approvals and widespread reimbursement will ultimately depend.

Valuation – our risked DCF model implies a 35 cps target price on a fully diluted basis. The key variables in the valuation are the choice of commercial pathway in major markets (direct sales versus distribution). Equity value could re-rate as the company passes quality and evidence gates: CE Mark in Q4; US pivotal trial design approval by the FDA in Q4; first commercial sales to EMEA in 2016. Our de-risked valuation for Oncosil is approximately 100 cps (upside case).

12-mth share price performance



	1-mth	6-mth	12-mth
Abs return (%)	61.5	84.5	40.9
Rel return (%)	59.6	90.6	42.5

Risks and catalysts

Catalysts: a) CE Mark; b) FDA trial guidance; c) EU marketing approval and first sales. **Risks**: a) access to capital; b) clinical trial design risk; c) regulatory risks; d) product safety/quality/logistics risks; e) sector sentiment.

Year-end June (AUD)	FY14A	FY15A	FY16F	FY17F	FY18F
NPAT rep ($m)	-4.2	-2.9	-6.1	-9.9	-8.5
NPAT norm ($m)	-4.2	-2.9	-6.1	-9.9	-8.5
Consensus NPAT ($m)					
EPS norm (cps)	-1.4	-0.8	-1.6	-2.2	-1.9
EPS growth (%)	-139.6	40.4	-97.4	-35.4	13.4
P/E norm (x)	-12.5	-21.0	-10.6	-7.8	-9.1
EV/EBITDA (x)	-8.9	-13.9	-6.9	-4.2	-4.9
FCF yield (%)	-10.5	-0.4	-10.6	-18.0	2.3
DPS (cps)	0.0	0.0	0.0	0.0	0.0
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0
Franking (%)	0	0	0	0	0

Source: Company data, WHTM estimates, S&P Capital IQ

KEY CHANGES		Before	After	Var %
NPAT:	**FY16F**		-6.1	
norm	**FY17F**		-9.9	
($m)	**FY18F**		-8.5	
EPS:	**FY16F**		-1.6	
norm	**FY17F**		-2.2	
(cps)	**FY18F**		-1.9	
DPS:	**FY16F**		0.0	
(cps)	**FY17F**		0.0	
	FY18F		0.0	
Price target:			0.35	
Rating:			**BUY**	

PRICE TARGET

	Valuation	Price target
WACC (%)	14	
Tg (%)	4	
NPV fcst FCF	21	
NPV perpetuity	94	
Net debt/(cash)	-5	
Valuation ($m)	120	
DCF ($/share)		0.24
HCC option ($/share)		0.11
Price target ($/share)		**0.35**
Un-risked valuation		**1.00**

INTERIMS ($m)

Half-year (AUD)	Dec 14 1HA	Jun 15 2HA	Dec 15 1HE	Jun 16 2HE
Sales revenue	0.0	0.0	0.7	0.8
EBITDA	-2.5	-0.6	-1.7	-4.4
EBIT	-2.5	-0.6	-1.7	-4.4
Net profit	**-2.5**	**-0.4**	**-1.7**	**-4.4**
Norm EPS	**-0.7**	**-0.1**	**-0.5**	**-1.1**
EBIT/sales (%)			-256.1	-586.9
Dividend (c)	0.0	0.0	0.0	0.0
Franking (%)	0.0	0.0	0.0	0.0

FINANCIAL STABILITY

Year-end June (AUD)	FY15A	FY16F	FY17F
Net debt	-2.5	-18.4	-7.5
Net debt/equity (%)	<0	<0	<0
Net debt/EV (%)	**<0**	**<0**	**<0**
Current ratio (x)	16.6	33.0	14.8
Interest cover (x)	19.9	78.5	33.1
Adj cash int cover (x)	**2.4**	**82.7**	**36.4**
Debt/cash flow (x)	0.0	0.0	0.0
Net debt (cash)/share ($)	<0	<0	<0
NTA/share ($)	0.0	0.1	0.0
Book value/share ($)	0.0	0.0	0.0
Payout ratio (%)	0	0	0
Adj payout ratio (%)	0	0	0

EPS RECONCILIATION ($m)

	FY15A		FY16F	
	Rep	Norm	Rep	Norm
Sales revenue	0	0	1	1
EBIT	-3.0	-3.0	-6.2	-6.2
Net profit	**-2.9**	**-2.9**	**-6.1**	**-6.1**
Notional earn	0.0	0.0	0.0	0.0
Pref/conv div	0.0	0.0	0.0	0.0
Profit for EPS	**-2.9**	**-2.9**	**-6.1**	**-6.1**
Diluted shrs (m)	355	355	380	380
Diluted EPS (c)	**-0.8**	**-0.8**	**-1.6**	**-1.6**

RETURNS

	FY15A	FY16F	FY17F	FY18F
ROE (%)	-30.1	-48.0	-73.3	-201.1
ROIC (%)	-30.6	-193.6	-1,352.6	154.3
Incremental ROE	293.8	-103.1	-486.0	-14.4
Incremental ROIC	125.0	46.6	164.8	-23.9

KEY ASSUMPTIONS

Year-end June (AUD)	FY13A	FY14A	FY15A	FY16F	FY17F	FY18F	FY19F	FY20F
Revenue growth (%)	-100.0				41.4	54.0	228.2	50.0
EBIT growth (%)	-104.9	382.6	-35.9	103.3	65.0	-14.9	-38.8	-121.9
NPAT growth (%)	-105.1	379.7	-31.7	111.3	62.1	-13.4	-39.7	-123.6
EPS growth (%)	**-101.9**	**139.6**	**-40.4**	**97.4**	**35.4**	**-13.4**	**-39.7**	**-123.6**
EBIT/sales (%)				-431.4	-503.5	-278.1	-51.9	7.6
Tax rate (%)	0.0	6.9	0.0	0.0	0.0	0.0	0.0	0.0
ROA (%)	**-15.7**	**-38.5**	**-40.9**	**-50.2**	**-118.5**	**-106.1**	**-76.3**	**14.8**
ROE (%)	**-14.5**	**-34.7**	**-41.4**	**-59.4**	**-180.7**	**366.7**	**164.9**	**-62.1**

PROFIT AND LOSS ($m)

Year-end June (AUD)	FY13A	FY14A	FY15A	FY16F	FY17F	FY18F	FY19F	FY20F
Sales revenue	0.0	0.0	0.0	1.4	2.0	3.1	10.2	15.3
EBITDA	-1.0	-4.7	-3.0	-6.1	-10.1	-8.6	-5.2	1.2
Depn & amort	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1
EBIT	**-1.0**	**-4.7**	**-3.0**	**-6.2**	**-10.2**	**-8.7**	**-5.3**	**1.2**
Net interest expense	-0.1	-0.2	-0.2	-0.1	-0.3	-0.1	-0.1	-0.1
Tax	0.0	-0.3	0.0	0.0	0.0	0.0	0.0	0.0
Minorities/pref divs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Equity accounted NPAT	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (pre-sig items)	**-0.9**	**-4.2**	**-2.9**	**-6.1**	**-9.9**	**-8.5**	**-5.2**	**1.2**
Abns/exts/signif	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reported net profit	**-0.9**	**-4.2**	**-2.9**	**-6.1**	**-9.9**	**-8.5**	**-5.2**	**1.2**

CASH FLOW ($m)

Year-end June (AUD)	FY13A	FY14A	FY15A	FY16F	FY17F	FY18F	FY19F	FY20F
EBITDA	-1.0	-4.7	-3.0	-6.1	-10.1	-8.6	-5.2	1.2
Interest & tax	-0.1	-0.2	2.8	-0.1	-0.3	-0.1	-0.1	-0.1
Working cap/other	0.6	-1.4	0.1	0.2	-0.2	10.3	-0.3	-0.4
Operating cash flow	**-0.5**	**-6.4**	**-0.2**	**-6.0**	**-10.7**	**1.6**	**-5.7**	**0.8**
Maintenance capex	0.0	0.0	0.0	-0.4	-0.2	-0.2	-0.2	-0.2
Free cash flow	**-0.5**	**-6.4**	**-0.2**	**-6.4**	**-10.9**	**1.4**	**-5.9**	**0.6**
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Growth capex	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Invest/disposals	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other inv flows	-0.2	-4.7	0.0	0.0	0.0	0.0	0.0	0.0
Cash flow pre-financing	**-0.7**	**-11.1**	**-0.2**	**-6.4**	**-10.9**	**1.4**	**-5.9**	**0.6**
Funded by equity	1.8	10.3	0.0	17.5	0.0	0.0	0.0	0.0
Funded by debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Funded by cash	-1.1	0.8	0.2	-11.1	10.9	-1.4	5.9	-0.6

BALANCE SHEET SUMMARY ($m)

Year-end June (AUD)	FY13A	FY14A	FY15A	FY16F	FY17F	FY18F	FY19F	FY20F
Cash	3.5	2.7	2.5	18.4	7.5	8.9	3.0	3.5
Current receivables	0.0	0.1	0.1	0.2	1.0	1.0	2.2	3.1
Current inventories	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.2
Net PPE	0.0	0.0	0.1	0.4	0.6	0.7	0.9	1.0
Investments	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Intangibles/capitalised	2.6	2.6	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	6.7	4.8	0.0	0.0	0.0	0.0	0.0
Total assets	**6.2**	**12.3**	**7.4**	**18.9**	**9.1**	**10.6**	**6.2**	**7.8**
Current payables	0.1	0.0	0.2	0.3	0.3	0.4	1.1	1.5
Total debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other liabilities	0.1	0.1	0.3	0.3	0.3	10.3	9.3	8.3
Total liabilities	**0.2**	**0.1**	**0.4**	**0.6**	**0.6**	**10.7**	**10.3**	**9.8**
Minorities/convertibles	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Shareholder equity	**6.1**	**12.2**	**7.0**	**18.4**	**8.5**	**0.0**	**-4.2**	**-2.0**
Total funds employed	**6.1**	**12.2**	**7.0**	**18.4**	**8.5**	**0.0**	**-4.2**	**-2.0**

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Investment view – Oncosil Medical

Investment summary

Oncosil is a developmental stage medical device business designing products for cancer treatment

Oncosil Medical is an Australian medical device company developing an implantable, radioactive treatment for addressing inoperable pancreatic and liver cancers. Tumour-directed, internal radiation therapies have shown to be a valuable means of treating cancer in both the prostate and liver cancer settings (notably by Sirtex Medical). Oncosil's extension of "brachytherapy[1]" into the pancreatic arena is timely, given the exceedingly poor prognosis associated with that disease[2]. The product has been tested in small, uncontrolled studies in two tumour settings, with favourable results[3]. Oncologists say they want a safe means of controlling aggressive primary pancreatic tumours, as an adjuvant to chemotherapy. Oncosil is contemplating two watershed moves for its business over the next 12 months: formal marketing clearance in Europe and the start of a registration-directed clinical trial in the US. We initiate coverage with a SPECULATIVE BUY rating and 35 cps price target.

Investment merits

- **Clear product specification and functional evidence** – we think the opportunity to safely deliver a large dose of radiation to primary tumours, with precision, in the earliest stages of treatment, is attractive. De-escalation of primary tumours may have clear consequences for patients in terms of pain reduction and the risk of metastatic development and death.

  Elegant product concept

- **An oncology story with an uncomplicated competitive landscape** – the treatment options in pancreatic cancer are less complicated than in other cancers. Accordingly, the development pathway for Oncosil is relatively straightforward to map. The standards of care in pancreatic cancer are unlikely to change materially, given how refractory this cancer has proven to both systemic chemotherapy and investigational, targeted drugs. The comparative data contemplated by Oncosil's planned pivotal trials will have long-dated clinical relevance, in our view.

  Pancreatic cancer treatment options are straightforward and limited – good competitive opportunity for Oncosil

- **FDA's accelerated review guidance for medical devices an opportunity to seek approval on tumour response activity** – the FDA has very recently announced a new medical device approval pathway for "breakthrough" treatments. Hitherto, accelerated programs were only available for drugs and not devices. This is a timely change which Oncosil may choose to pursue.

  FDA offering "accelerated" pathways for medical devices

- **Straightforward approach to pricing and cost-effectiveness** – we expect that Oncosil will seek pricing in line with external beam radiation, which is already widely used in pancreatic cancer. Sirtex took a similar approach to reimbursement in its early days. In time, Oncosil should seek more specific forms of coding and reimbursement to increase value; which should be straightforward if the product proves to be efficacious and safe.

  Reimbursement strategy is uncontroversial

- **An obvious and necessary clinical "fit" with current treatment plans** – the potential advantage over available radiation modalities is so profound that OncoSil™ could slot very easily into clinical practice as an alternative to external beam procedures. As it is delivered in only one session and is procedurally simple, OncoSil™ could be deployed very early post-diagnosis, as an adjuvant to first lines of chemotherapy.

  Single injection, relatively simple work-up and procedure

- **Investigator interest** – great therapies and devices are those that develop an investigator-led following, independently of the manufacturer. Although the product might only develop a handful of formal approved indications, the intellectual curiosity and support of medical oncologists and interventional radiologists may take demand in unexpected directions, addressing other tumours. A high level of evidence will be needed in order to be "practice changing" for the early majority of adopters.

[1] A form of radiotherapy where the radiation source is placed a short distance from the tumour, often internally. Brachytherapy devices have been developed for locally confined cancers, in the main – with cervix, prostate and liver being good examples.
[2] See National Cancer Institute: http://seer.cancer.gov/statfacts/html/pancreas.html which estimates 5-year survival of 7.2%.
[3] For liver results see Goh, A. S. *et al.* (2007) *A novel approach to brachytherapy in hepatocellular carcinoma using phosphorous32 brachytherapy delivery device – a first in man study.* Int. J. Rad. Onc. Biol. Phys. **67**: 786 – 792. Pancreatic results are available in OncoSil's investor materials, with a manuscript in preparation for peer reviewed publication.

What are the risks?

- **Clinical trial risks** – the failure to show a clean signal in clinical trials can lead to years of delay, as those trials are re-designed (often explored in different patient groups, measuring different clinical endpoints) or simply repeated. Worse, clinical programs can be discontinued completely if the data is not strong enough to justify further advancement. Trials can fail on account of the product not being good enough, or through poor trial design and execution.
- **Commercial risks** – Oncosil will likely seek partnering or out-licensing arrangements in the major markets. The commercial risks include: continuity of supply of key input materials (radioactive phosphorous, silicon); a single product model means concentrated exposure to product safety issues; regulatory compliance risks as a manufacturer of a pharmaceutical product where quality/safety requirements are very stringent; logistics and supply chain risks; intellectual property risks including the defence/infringement of exclusive patent rights and trademarks; competitive obsolescence resulting from other approaches to treating advanced pancreatic cancer; reimbursement risks may impact the affordability of the treatment for patients, reducing demand.
- **Level 1 evidence not in place** – Oncosil must generate a higher level of evidence in order to achieve major marketing clearances and widespread reimbursement. Their current Phase I/II evidence does not qualify, but the planned pivotal study will, if successful.
- **Competitive technology risks** – oncology is a crowded field, technologically speaking. Several new "immuno-oncology" treatments have achieved brilliant results, but so far this has been limited to haematological malignancies and melanoma. Immune-based therapies take several months of treatment before any benefit is seen, and don't shrink solid tumours. We think pancreatic primary tumours are likely too aggressive and invasive to be treated in this manner. The combination of radiotherapy and chemo/targeted therapies should remain the dominant treatment paradigm, in our view.
- **Valuation risk** – our DCF valuation implies successful development and commercialisation outcomes, all of which are uncertain. Although we are confident that our forecasts are based on realistic estimates of market size and future competitive dynamics, the adoption of new medical devices is difficult to forecast. The choice of discount rate attempts to control for these risks and uncertainties, but may prove inadequate.
- **Financial risk** – as at 30 June 2015 Oncosil reported ~$7m in cash and no debt. Oncosil will likely require new capital to finance its pivotal US clinical trial but faces no urgency in that. The ability to raise capital and the issue price of new capital does affect valuation in per share terms. We have made allowances for this and present our valuations on a fully diluted basis.
- **Intellectual property risks** – the current OncoSil™ product is protected by certain patent rights, although subsequent generations/variants of the product may be contemplated. We have not conducted any analyses of freedom to operate or patent validity. Other forms of intellectual property and know-how impose barriers to entry that would be challenging but not impossible to overcome.
- **What the Oncosil bears say** – the contra arguments most often relate to Oncosil's proposed clinical trial design, in that it seeks to establish a "surrogate" endpoint and not a higher-level endpoint such as overall survival. We are comfortable with the proposed trial design as we understand it, because it appears to be consistent with the FDA's new guidance on "accelerated" approvals for medical devices. Oncosil has yet to announce the details of its US regulatory strategy.

  We think that Oncosil should, in the future, sponsor at least two further trials – a large study confirming an overall survival benefit compared to standard of care; and another comparing OncoSil™ head to head with other radiotherapy techniques. But neither of these studies is necessary to obtaining first US approval and marketing clearance, in our view.

Valuation

DCF valuation

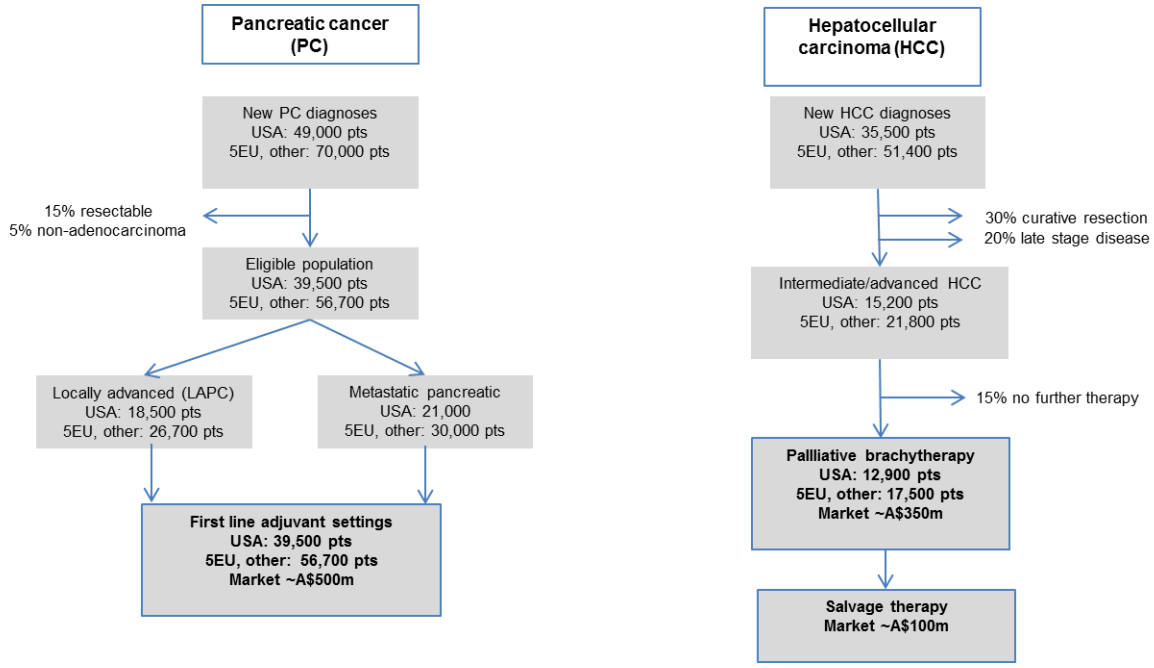
We model developed market PC and HCC populations using the best available epidemiological data points

Forecasting basis – our valuation for Oncosil is based on a discounted cash flow (DCF) methodology as this is best able to capture the expected growth, capital intensity, risks and future optionality. We have developed an explicit forecast for OncoSil™ sales across three segments of the global cancer market: US, five EU (UK, France, Germany, Italy and Spain) and APAC (principally Australia and New Zealand).

Price target set at 35 cps on a fully diluted, risked basis

We have developed population based models for both pancreatic and liver cancers in these markets, extending to 2030. Incidence data (number of new cases in each country each year) suggests ~49,000 newly diagnosed cases of pancreatic cancer each year in the US. Hepatocellular carcinoma (HCC) is relatively uncommon in the US and most of Europe, although its incidence is rising due to hepatitis C (HCV) infection[4] and the widespread, untreated prevalence of non-alcoholic steatohepatitis (NASH). HCC rates are far higher in the developing world. We estimate ~35,500 new primary HCC cases in the US, annually. Our forecasting assumptions are described in more detail in the Financials section of this report.

Figure 1: Populations in the developed world markets



Source: WHTM Research

The marketing challenge will be to convince medical oncologists to refer pancreatic cancer patients earlier to interventional radiologists

Diffusion into pancreatic and HCC likely to be slow initially, but nonetheless meaningful – while it is difficult to forecast uptake rates for new products, our first assumptions are based on OncoSil™ reaching ~30% of the eligible pancreatic cancer population in the US but just ~10% in European and ANZ markets. We assess a global peak annual sales target of in the order of A$350-400m treating pancreatic cancer. The opportunity in treating HCC is ~A$60m given the higher levels of competition and clinical complexity.

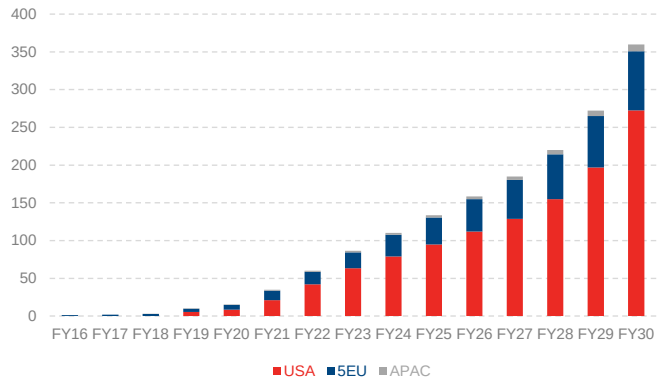
[4] See: http://www.cancer.gov/types/liver/hp/adult-liver-treatment-pdq

Table 1: Revenue model assumptions & forecast summary

Specific growth of pancreatic cancer incidence			1.0%
	USA	5EU	ROW
Incidence (new diagnoses per year in 2016)	48,960	67,761	100,000
ASP (US$, EUR and A$ per course)	15,000	8,000	6,500
Launch year	2019	2016	2016
Penetration 5yrs post launch	8.0%	0.8%	0.2%
Penetration 10yrs post launch	18.6%	4.2%	1.5%
Peak end-market sales (A$m)	**272.5**	**78.3**	**9.1**

Source: WHTM Research

Figure 2: Revenue model assumptions & forecast summary



Source: WHTM Research

Table 2: DCF parameter summary

Valuation		The Inputs	
PV of FCFF ($M) =	21.2	Forecast period	FY16-30E
PV of Terminal Value ($M) =	94.2	Risk-free rate	3.50%
Value of Operating Assets of the firm ($M)	115.5	Risk premium	7.00%
- Net Debt ($M)	(5.0)	Beta	1.2
Equity value ($M) =	**120.5**	Clinical risk adjustment	60%
Shares on issue	356.2	WACC	14%
New issuance and options	147.3	Tg	3.50%
Fully diluted shares	503.5		
Value of Equity per share =	**$0.24**		
Value of HCC option	**$0.11**		
OSL Target Price	**$0.35**		

Source: WHTM Research

Valuation upside a familiar story: de-risking the technology and lowering the discount rate as firm profitability approaches – we have assumed that Oncosil remains debt free but dilute the valuation for future capital requirements. We have recognised a near-term weighted average cost of capital (WACC) of ~14% which anticipates the company being granted CE Marking this year. Our terminal value is based on perpetuity growth rate of 3.5%, which reflects long-term growth in natural incidence and diagnosis rates for pancreatic and primary liver cancers in the developed world markets. The valuation is also adjusted for the risk of clinical failure by risking all future cash flows by 60%. If we "de-risked" the model (setting that adjustment factor to 100%) and valued the company using a WACC of 10% (more in line with Oncosil's obvious profitable peer, Sirtex) – our valuation would be **100 cps** on a fully diluted basis.

Valuation treatment of options to extend into liver and other "off label" cancer settings – no sales made outside pancreatic cancer are recognised in our forecasts or primary DCF valuation. Potential sales into liver cancer or any other "off label" settings for OncoSil™ are recognised as "growth options", which we value essentially as an NPV of after-tax cash flows that might be expected from commercialisation in those settings.

Relevant clinical settings described in brief

Pancreatic cancer

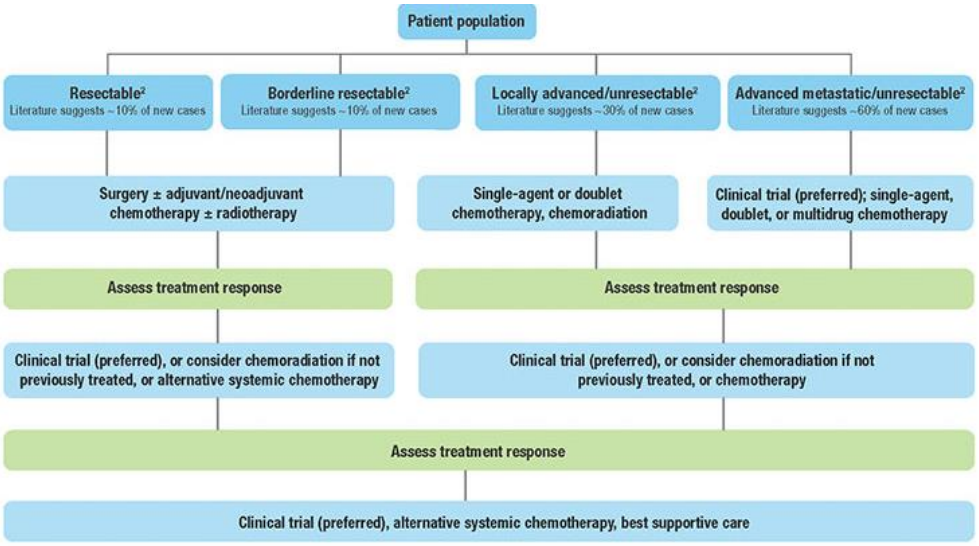
The pancreas is a small, glandular organ in the digestive system, which is located behind the stomach – it has dual functions. It is an endocrine gland producing peptide hormones like insulin and glucagon that regulate metabolism. The pancreas is also a source of digestive enzymes (produced by exocrine glands). The most common form of life threatening pancreatic cancer originates in the exocrine tissue – specifically, the gland cells. These pancreatic "adenocarcinomas" account for nearly 95% of cases, most often developing in the pancreatic ducts.

Late-stage presentation and poor prognoses – the pancreas is too deep inside the body for routine physical examination. Patients usually have no symptoms at all until the original tumour has either become locally advanced or has spread to other organs. As a result, pancreatic cancer has among the worst one and five-year survival rates of all solid tumour malignancies.

Disease staging – the stage of disease at diagnosis is the single most important factor in determining a treatment plan and predicting survival. Pancreatic cancer is staged using data from molecular diagnostics, imaging studies, endoscopies, ultrasound and biopsies.

Treatment options limited but well characterised – if the tumour is confined to the pancreas and a surgeon believes the entire tumour can be removed then that case is called resectable. Although potentially curative, this option is confined to perhaps 15% of newly diagnosed cases. Only two chemotherapy drugs (gemcitabine[5] and abraxane) have been shown to extend survival sufficiently to be considered standard of care. In countries where reimbursement access to gemcitabine/abraxane is limited, a drug combination known as FOLFIRINOX[6] is standard of care.

Figure 3: Schematic summarising the treatment pathways in pancreatic cancer



Source: US National Comprehensive Cancer Guidelines (NCCN)

There are few treatments available for the control of locally advanced or metastatic pancreatic cancer – adding external beam radiation to chemotherapy may achieve a level of pain relief but this is controversial in the case of unresectable, loco-regionally advanced disease[7].[8] The specific role of radiotherapy in controlling unresectable, loco-regionally advanced disease (shrinking tumours) remains controversial.

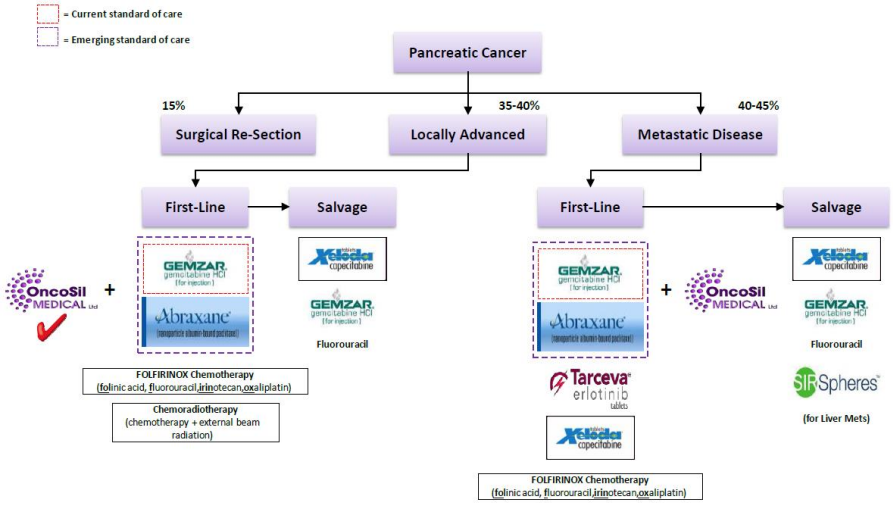
[5] Yip, D. et al. (2006) *Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer* Cochrane Database Syst. Rev. 3:CD002093.
[6] The FOLFIRINOX regimen comprises three drugs: folinic acid, irinotecan and oxaliplatin.
[7] Minsky, B. D. *et al.* (1988) *The role of radiation therapy in the control of pain from pancreatic carcinoma* J. Pain Sympt. Mgt. 3:199 – 205.
[8] Hazard, L. (2009) *The role of radiation therapy in pancreas cancer* Gastrointest. Cancer Res.

On the one hand, radiotherapy may slow the progression of local disease and possibly alleviate or prevent symptoms including pain, biliary obstruction, bleeding and bowel obstruction[9]. On the other hand, the likelihood of micro-metastatic, distant disease is very high, so treatment is not expected to be curative.

Pressing need for more aggressive and earlier therapies, which may further strengthen the case for a product like OncoSil™ – as a result of persistently inadequate local tumour control rates, consensus among practicing radiation oncologists has shifted away from electively treating loco-regional lymph nodes in order to focus dose-escalation efforts on the primary pancreatic tumour[10]. The primary tumour remains a prime target for therapy, even after metastatic spread. In approximately 30% of patients with unresectable tumours, the lesions remain locally advanced without evidence of distant metastases at autopsy[11].

The idea of simplifying and intensifying early chemo-radiation is attractive – over the past decade, medical oncologists have tended to refer patients to radiation later. The benefits of external beam are controversial, whereas the toxicities associated with it are not. Combining the initial 4-6 month course of chemotherapy with multiple sessions of radiation over a 5-6 week period (in parallel) can be very hard on patients, so the radiation component has tended to be deferred. More advanced radiation techniques have become available which achieve better margin control and lower concomitant tissue damage. The use of stereotactic body radiotherapy (SBRT)[12] delivers ablative doses of radiation to the gross tumour volume plus a small margin. SBRT has been shown to be effective in the treatment of several malignancies, including lung and pancreatic cancers, and has been found to be superior to dose-escalated fractionated radiotherapy. Whereas local control rates have essentially exceeded those seen with conventionally fractionated radiotherapy, toxicity rates in early reports of SBRT had also been correspondingly higher. For that reason perhaps, SBRT has not been able to reverse the trend to defer radiotherapy. Interventional radiologists we have spoken to say that there would be an obvious place for any product that could deliver an effective dose in one sitting, with less toxicity.

Figure 4: Oncosil is intended as an adjuvant therapy, to be given alongside first-line chemotherapy in unresectable, locally advanced pancreatic cancer



Source: Oncosil

[9] Loehrer, P. *et al.* (2011) *Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial*. J Clin Oncol. 2011;29:4105-4112.
[10] Huguet, F. *et al.* (2012) *Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations*. Int J Radiat Oncol Biol Phys. 83:1355-1364.
[11] Iacobuzio-Donahue, C. A. *et al.* (2009) *DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer* J. Clin. Oncol. 27: 1806 – 1813.
[12] SBRT uses imaging software to locate the target tumour (in some cases based on the position of implanted fiducial markers) and adjust the beam aim should any changes in target position be detected. The apparatus can track and automatically correct for respiratory motion while irradiating targets in lung, liver and the pancreas.

Availability of better guidance/placement technologies an important enabler – point-of care imaging systems and ultrasound-guided endoscopy equipment makes the delivery of loco-regional therapies easier. This is significant because OncoSil™ is injected via a retractable needle that is on the distal end of an endoscope (see an example at right). Placing OncoSil™ in the pancreas requires a similar level of training and skill to the placement of fiducial markers that assist external beam radiation therapy[13].

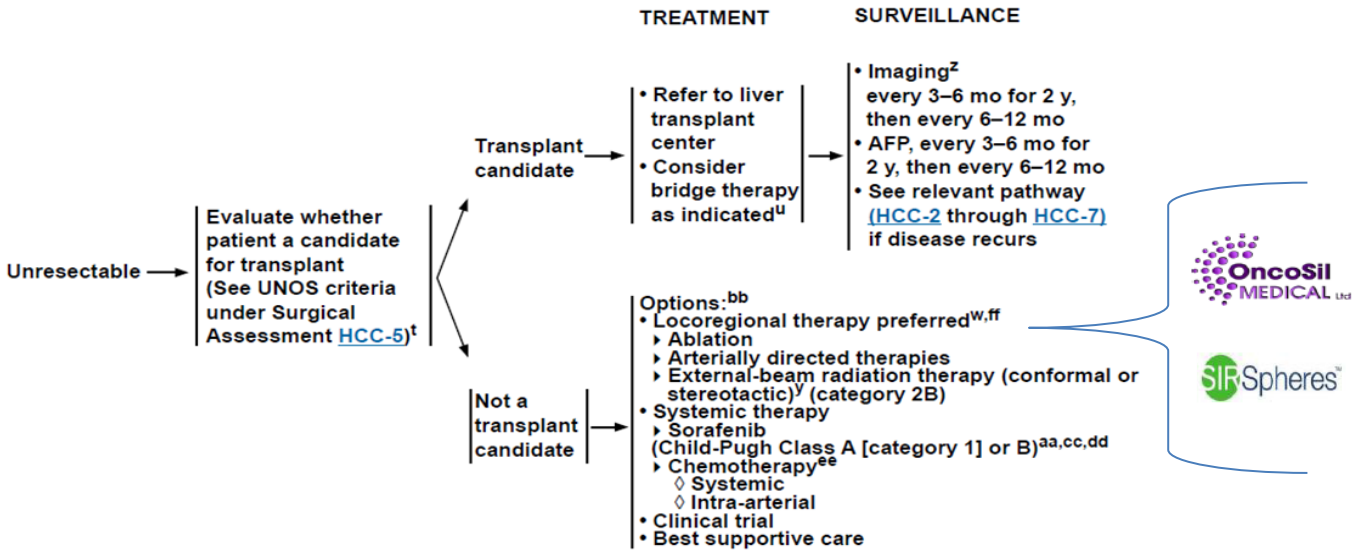
Liver cancer

Liver tumours can arise either as primary liver cancer or by metastasis to the liver from other tissues or organs. In the former, hepatocellular carcinoma (HCC) is the most common form accounting for 90% of primary liver cancers. The worldwide prevalence of HCC is expected to increase, driven by a number of risk factors such as hepatitis B/C viral infection, liver cirrhosis (alcohol related) and the development in non-alcoholic steatohepatitis (NASH, in turn caused by diabetes and obesity. HCC is a complex disease to treat, as it is actually two disorders combined: the cancer and underlying damaged liver tissue. Most patients with HCC are diagnosed with advanced disease, limiting potential cure via surgical resection or transplantation.

Current treatment options for various stages of the disease include:

- Very early stage: Surgical resection; ~15-20% of new cases;
- Early stage: Liver transplantation, radio-frequency ablation (RF) or percutaneous ethanol injection (PEI); ~15-20% of new cases;
- Intermediate to advanced stage: Non-curative, palliative treatment; 50-60% of new cases;
- Transarterial chemoembolisation (TACE)/ transarterial embolisation (TAE);
- Nexavar (Sorafenib), a chemotherapy agent; and
- Selective internal radiation therapy (SIRT).

Figure 5: OncoSil™ could find usage in similar settings to Sirtex's SIR-Spheres in the first-line treatment of unresectable HCC, where loco-regional therapies are preferred over systemic chemotherapy



Source: NCCN, WHTM Research

[13] Fiducial markers are radio-opaque objects placed to help accurate delivery of radiation to specific structures.

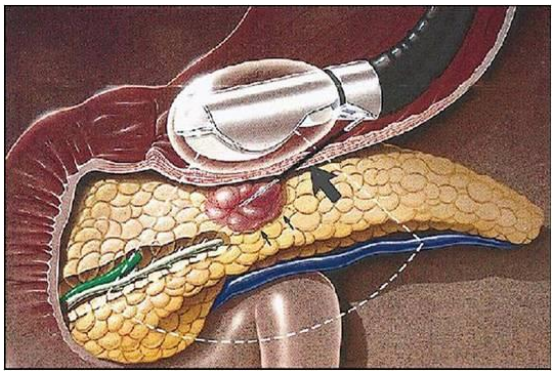
Company overview

Oncosil is an emerging medical device company based in Sydney – the OncoSil™ technology has its origins in the UK, where it was originally developed by QinetiQ, a British defence technology company. Certain nanotechnologies relating to drug delivery were transferred to pSivida Corporation (PVA). pSiMedica, a subsidiary of pSivida, developed a product called BrachySil, which was later renamed OncoSil™. The product's early preclinical development was conducted by a UK company called Enigma Therapeutics under a worldwide exclusive licence from pSiMedica. In 2012, ASX-listed company Neurodiscovery (NDL) acquired 100% of Enigma Therapeutics and renamed the entity Oncosil Medical.

Product characteristics and usage

OncoSil™ – the product is a suspension of silicon microparticles, approximately 30 microns in diameter, which are loaded with a radioactive isotope of phosphorous, P^{32}. The manufacturing process uses an acid-etching step to alter the surface characteristics of the particles, such that they are rendered "sticky" and tend to be retained in the tissues to which they are delivered. OncoSil™ is designed for direct injection into tumours, preferably at a number of sites, using an endoscope equipped with a type of syringe. Introduced orally, these long endoscopes are advanced (guided by ultrasound imaging) far enough down the gut to access the pancreas and its structures, adjacently, by injecting through the gut wall.

Figure 6: OncoSil™ is delivered directly to the tumour's blood supply using ultrasound guided endoscopy. The particles irradiate tumours internally, which may be preferable to external beam radiation



Source: OncoSil Medical, WHTM Research

Once injected into the tumour OncoSil™'s field of emitted radiation is very uniform, intense and predictable, so a number injections can be placed in one sitting, so as to maximise tumour coverage and overlap. The injected isotopes emit internal radiation for 12 weeks post-implantation, killing cells indiscriminately. The cell death thus induced can exert other forms of intra-tumoural killing for weeks. Importantly, because radiation is only emitted over very short distances, the healthy, surrounding tissues can be spared from radiation. The radioactivity emission is also finite. Once the isotopes decay, the spent silicon microparticles are not removed – they are left inside the pancreas as an inert residue.

Is OncoSil™ easy to deliver? Manual dexterity and experience with ultrasound guided endoscopes is mandatory. Care must be taken to avoid deploying the injection apparatus inappropriately and perforating the gut. Positioning the implant also demands great precision, particularly in cases where the tumour is very close to the stomach or other structures, where the risk of tissue damage and/or ulceration is high. Centre training by Oncosil will guide radiopharmacists and interventional radio-oncologists in the deployment of OncoSil™ in pancreatic and liver tumours. Training and certification programs are to be designed and supervised by Oncosil's Chief Medical Officer.

Who are the future users and who are the gate-keepers? Oncosil will be a tool for interventional radiologists who make the pancreas a focus. Widespread adoption will require support from a different set of doctors – the medical oncologists. These individuals are often the first specialist physicians to see pancreatic cancer patients post diagnosis and practitioners of chemotherapy. These doctors need to be persuaded that OncoSil™ is safe and effective enough to make earlier referrals to interventional radiologists.

Will the case work-up be prohibitively complicated? We view OncoSil™ therapy as a relatively straightforward procedure. As in many areas of oncology practice, a relatively high level of consultation and collaboration will be required between medical oncologist(s), interventional radiology and nuclear medicine. Pancreatic tumour staging is relatively rapid and depends heavily on accurate imaging (CT scanning, transcutaneous ultrasonography, endoscopic ultrasonography, magnetic resonance imaging and positron emission tomography). Often multiple imaging techniques are required to assess the prospect of resection, proximity to the bowel/stomach which can rule out external beam radiotherapy or to provide a differential diagnosis excluding chronic pancreatitis.

What is the current level of evidence?

Evidence is low level, but sufficient for CE Mark and admission to pivotal Phase III trials – the product has been tested in four small, uncontrolled clinical trials looking at pancreatic and primary liver cancer. Data for these studies was presented at the 2008 meeting of the American Society of Clinical Oncology (ASCO). Note that Oncosil is not the first radiation-based implant to be tested in the pancreatic setting. Previous attempts, mainly by academic investigators, have used isotopes like I^{130} but without dramatic success.

Table 3: Only a small number of small clinical trials have attempted to treat pancreatic cancer with brachytherapy approaches other than OncoSil™

Study	Therapy	n	Response (%)	Adverse Events
Sun et al. (2005)[14]	Iodine seeds implantation	15	Partial (27) Minimal (20) Stable (33) Progression (20)	Pancreatitis, pseudocyst, neutropenia, anaemia
Jin et al. (2008)[15]	Iodine seeds + chemotherapy	22	Partial (13) Stable (46) Progression (41)	Hyperamylasemia, mild fevers, seed translocation
Guo et al (2009) Wang et al (2013)[16]	Iodine seeds	1	Complete remission	None
Zhang et al (2004)[17]	Stenting, after-loaded with brachytherapy	49 (6 pancreas)	Study concluded brachytherapy pts did better than not	
Liu et al. (2009)[18]	Radioactive stents	11	Stable (73) Progression (27)	None
Ross, P. J. et al (2008)[19]	OncoSil + gemcitabine	17	Partial (12) Stable (71) Progression (6)	Neutropenia (Grade 3 toxicity – 23%)

Source: WHTM Research

Evidence in the pancreatic setting – two small pilot studies have been conducted in patients with locally advanced pancreatic cancer (Table 4). The first was a single intra-tumoural injection of OncoSil™ manufactured at a dose intensity of 100 Gy[20] . Patients were also given standard of care gemcitabine within two weeks prior or three days following OncoSil™.

[14] Sun. S. *et al.* (2006) *EUS-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial*. Endoscopy. 38: 399 – 403.
[15] Jin, Z. et al. (2008) *EUS-guided interstitial implantation of iodine 125 seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study*. Endoscopy 40: 314-320.
[16] Wang, H. *et al*. (2013) *The investigation of 125I seed implantation as a salvage modality for unresectable pancreatic carcinoma* J. Exp. Clin. Cancer Res. 32:106
[17] Zhang, FJ et al (2004) Clinical value of brachytherapy of malignant biliary obstruction after implanting expandable metallic biliary endoprothesis (EMBE) – [Article in Chinese] Ai Zheng. 23(11 Suppl):1567-71.
[18] Liu, Y. et al. (2009) Intraluminal implantation of radioactive stents for treatment of primary carcinomas of the peripancreatic-head region. Gastr. Endosc. 14: 3798 – 803.
[19] Ross, P. J. et al. (2008) Novel delivery via endoscopic ultrasound of a 32-P brachytherapy device in addition to gemcitabine in advanced pancreatic cancer. Abstract #205 ASCO Gastrointestinal Cancers Symposium Jan-26 Orlando Florida.
[20] The Gy (or Gray) is a unit of ionising radiation dose defined as the absorption of one joule of radiation energy per one kilogram of matter.

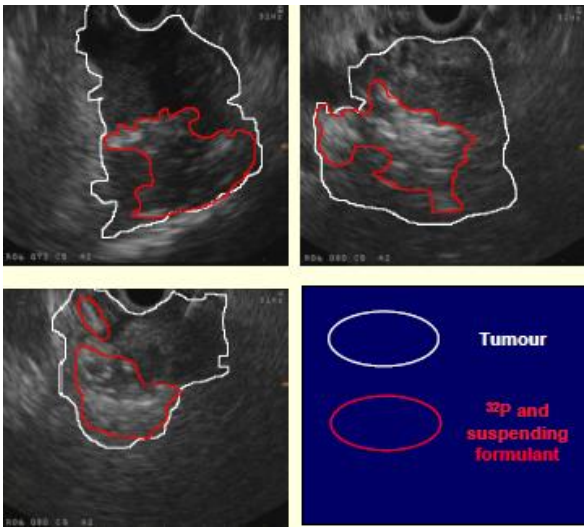
Key findings

Activity confirmed at target tumour sites – >80% of treated patients experienced a reduction in target tumour volumes. Only two of the responders (2%) experienced less than 15% reductions in tumour volume; and 50% of responders achieved target tumour volume reductions greater than 30% (overall study median was 33% reduction).

Disease control – 12 patients were evaluable for response with 2 (12%) achieving partial response and 9 (53%) stable disease. Median progression free survival was 121 days. Median overall survival (OS) was 309 days or 10+ months, which compared well with a) gemcitabine monotherapy trials in advanced cancers which achieved OS outcomes of ~5-6 months[21]; and b) gemcitabine/abraxane combo trials which achieved OS of ~8-9 months[22].

Safety – implantation via endoscope was well tolerated with no complications. There were no significant safety problems related to OncoSil™ during the studies. The expected level of gemcitabine-related toxicity was seen, but there was no clinically significant increase. Urinary excretion of radioactive P^{32} was detected in 6 (35%) of patients; stool excretion in 9 (53%) of patients; and in the blood of 1 (6%) of patients.

Figure 7: Ultrasound images illustrating the successful injection of OncoSil™ into pancreatic tumour masses



Source: Ross (2008)

Table 4: Only a small number of small clinical trials have attempted to treat pancreatic cancer with brachytherapy approaches

Study	Details	n	Response (%)	Adverse Events
BIOSP-201 (2005)[23]	Single dose, single centre open label safety study in hepatocellular carcinoma (HCC)	8	Complete (25) Partial (25) Stable (38) Progression (13)	No Grade 3 or 4 toxicities related to OncoSil™
BIOSP-202 (2006)	Multi-centre, dose escalating study in HCC	11		
DB2-201 (2008)	Multi-centre, open label, dose escalating study in locally advanced pancreatic cancer	17	Partial (12) Stable (71) Progression (6)	Neutropenia (Grade 3 toxicity – 23%)
DB2-202 (2009)[24]	Multi-centre, open label, dose escalating safety study (200 to 400 Gy) in locally advanced pancreatic cancer	6	Stable (100)	No Grade 3 or 4 toxicities related to OncoSil™

Source: Oncosil, clinical studies, WHTM Research

Evidence in the HCC setting – for the treatment of liver cancer, OncoSil™ was administered as either a single injection through the lining of the abdomen, directly into tumours, under local anaesthesia. The only published work reported that implantations were successfully performed with no serious adverse events attributable to OncoSil™. Twelve weeks after implantation, all targeted tumours were responding with 100% tumour shrinkage in three lesions. At the end of the study (24 weeks post-implantation), there were 2 (25%) complete responders, 2 (25%) partial responders and three patients (38%) with stabilised disease.

Table 5: Tumour responses in HCC pilot trial (n=8)

Patient	Tumour Shrinkage	Response
001	-44%	Stable
002	-80%	Partial
003	-16%	Stable
004	-43%	Partial
005	-100%	Complete
006	-100%	Complete
007	-100%	Complete
008	-35%	Stable
Median	-62%	n/a

Source: Oncosil, WHTM

[21] In the Phase III randomised ECOG-6201 trial two different gemcitabine monotherapy regimens were tested head to head, treating patients with advanced pancreatic cancer. Median overall survival was 6.2 months and 4.9 months in respective arms. See: Poplin, E. *et al.* (2009) *Phase III randomised study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30 minute infusion) in patients with pancreatic carcinoma*. J. Clin. Oncol. 27: 3778 – 3785.

[22] Phase III MPACT trial in 861 metastatic patients without prior chemotherapy showed 6.7m survival for gemcitabine and 8.7m when abraxane was added. See Von Hoff, D. D. *et al.* (2013) *Increased survival in pancreatic cancer with nab-placlitaxel plus gemcitabine*. NEJM 369: 1691 – 1703.

[23] Goh, A, S. *et al.* (2007) *A novel approach to brachytherapy in hepatocellular carcinoma using a phosphorous-32 brachytherapy delivery device – a first in man study*. Int. J. Rad. Onc. Biol. Phys. 67: 786 – 792.

[24] Six patients were studied at two centres in the UK (Guy's and St Thomas' NHS Foundation Trust and University Hospital, Birmingham).

What new OncoSil™ clinical trials are planned?

Phase III pivotal study in 225-275 patients is the benchmark for first US approval – Oncosil is classified as a Class III medical device and as such is only approvable in the US via the Pre-market Authorisation (PMA) pathway. A PMA application is built on high level evidence, collected in well-designed studies, preferably randomised controlled trials (RCTs), measuring clinically meaningful endpoints in a statistically significant manner. To conduct such trials in the US, companies must first obtain permission to use their un-approved or investigational device in people – under what is known as an Investigational Device Exemption (IDE). In other words, the FDA must approve the proposed trial before any clinical activities can commence. Oncosil will very soon formally open the dialogue with the FDA about its proposed IDE trial. Investors should understand all facets of this process and the potential outcomes – which determine the viability of the project.

We expect to see a pilot trial first, followed by a pivotal phase – it is very common for the FDA to ask companies to conduct a "pilot" phase of the trial, which can then segue into a full "pivotal" phase that ultimately confirms efficacy and safety. Pilot phases allow the FDA to monitor early safety for new devices. Equally, pilot results can be used to specify the statistical design for the pivotal phase: expected effect size, correct number of patients, endpoints, statistical analysis plan etc.

Local, progression free survival in the pancreas is particularly important for Oncosil – High quality, Level 1 evidence around this "surrogate endpoint" can be a powerful outcome. This endpoint it both potentially registrable and would be very persuasive, clinically; particularly once the result is confirmed by a peer review process, such as publication in a leading journal (eg *Journal Clinical Oncology*) or acceptance at a scientific conference such as the American Society of Clinical Oncology's (ASCO) annual meeting.

Much value in pursuing overall survival (OS) data later – a trial with an OS objective would take several years to complete, enrol between 750-1,000 patients (WHTM estimates) and cost $30-40m. Given the seriousness of cancer as a disease and the related pressure to make new therapies available, the FDA has for more than 20 years made an "accelerated approval" pathway available to drug developers. The majority of cancer therapies now on the market won their first FDA approvals via this pathway. Unfortunately for medical device developers, the FDA only introduced and "accelerated" pathway to approval in April 2015.

Table 6: Recent and past FDA oncology drug approvals on surrogate endpoints via accelerated approval pathways

Drug	Sponsor	Indication	Primary Endpoint	Secondary Endpoints	Trial Design	AdCom
2015						
T-VEC	Amgen	Melanoma	Durable tumor response	OS w ith interim analysis	Phase III, double blinded RCT	22 - 1
Farydak	Novartis	Multiple myeloma	PFS	OS	Phase III, double blinded RCT	2 - 5
Ibrance	Pfizer	Metastatic breast cancer	PFS	OS, OR, Duration	Phase III, double blinded RCT	n/a
Unituxin	United Therapeutics	Neuroblastoma	Event free survival	PFS, tumor regression, OS	Phase III, open label, randomised	n/a
2014						
Beleodaq	Spectrum	Refractory peripheral T-cell lymphoma	Overall response rate	Duration of response	Phase II, open label, single arm, non-randomised, n=129	n/a
Blincyto	Amgen	B-cell acute lymphoblastic leukemia	Complete remission	Duration of response	Phase II, open label, single arm, non-randomised, n=185	n/a
Keytruda	Merck	Advanced melanoma	PFS	OS	Phase III, double blinded RCT, n=411	n/a
Lynparza	AstraZeneca	Advanced ovarian cancer	PFS	OS, biomarkers, best response	Randomized, double-blind, placebo-controlled	2 - 11
Opdivo	BMS	Advanced melanoma	Objective response rate (tumoral)	OS, PFS	Efficacy - 120 pts. Safety - 268 treated pts.	n/a
Zydelig	Gilead Sciences	B-cell lymphomas	PFS	OS, CR, lymph node R	Phase III, double blinded RCT	n/a
2013						
Imbruvica	Pharmacyclics	Mantle cell lymphoma	ORR	Duration of response	Open label, Phase II, single-arm n = 111	n/a
Pomalyst	Celgene	Multiple myeloma	ORR	PFS	Open label, Phase II, single-arm n = 221	n/a
Perjeta	Roche	HER2 +ve breast cancer	Pathological complete response	clinical response, time to resp.	Phase II, randomised, open label n=400	13 - 0
2012						
Kyprolis	Onyx/Amgen	Multiple myeloma	ORR	OS, Duration	Open label, single arm Phase II	11 - 0
Synribo	Cephalon/TEVA	CML	Major haematologic response	PFS	Open label, single arm Phase II/III	1 - 7
Iclusig	Ariad	CML	Major haematologic response	PFS, OS	Open label, single arm Phase II	n/a
Older						
Iressa	AstraZeneca	3rd line NSCLC	Tumor response			
Gleevec	Novartis	Unresectable GI tumor	Tumor response			
Temodar	Merck	Anaplastic astrocytoma	Tumor response			
Doxil	Janssen	Refractory ovarian cancer	Tumor response			
Doxil	Janssen	Kaposi sarcoma	Tumor response			
Eloxatin	Sanofi	2nd line colorectal cancer	Tumor response			
Xeloda	Genentech	Refractory breast cancer	Tumor response			
Camptosar	Pfizer	2nd line colorectal cancer	Tumor response			
Taxotere	Rhone-Poulenc	2nd line breast cancer	Tumor response			

Source: FDA, WHTM Research

New accelerated approval pathway for medical devices suits OncoSil™ development – in April this year the FDA finalised an "Expedited Access Pathway" program, or EAP to "help assure predictable, efficient, transparent and timely device assessment and review". An approval through the EAP will rely on less evidence than would ordinarily be required for approval. That means the FDA is likely to approve on "lesser" endpoints – provided companies agree to conduct rigorous post-market surveillance and in many cases longer clinical trials to establish the clinical benefit unequivocally.

The FDA's guidance says it will only permit devices which are "intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition". In addition, the device will need to meet at least one of three criteria:

- The device represents a breakthrough technology that provides a clinically meaningful advantage over existing legally marketed technology.
- No approved alternative treatment or means of diagnosis exists.
- The device offers significant, clinically meaningful advantages over existing legally marketed alternatives.

Endpoints… what should Oncosil measure as a priority? The ability to control or better, shrink, primary pancreatic tumours. There are potential pitfalls in how best to pre-specify what this means and how it is measured – but this general objective is the number one problem that pancreatic medical oncologists and patients face. Even after the point of metastasis, when the tumour has spread to other organs, the primary tumour remains both lethal and the principal cause of intractable, severe pain. Local progression free survival in the pancreas is both a significant and appropriate surrogate endpoint for a device like OncoSil™.

The question of overall survival? – in the majority of cases, the ultimate endpoint in cancer trials is overall survival (OS). A drug or device meeting this endpoint has essentially proven that it provides an indisputably lower risk of death by any cause, compared with other treatments. OS will always be the "high court" of cancer endpoints. There are many lesser endpoints that interest oncologists, are clinically important and are examined in cancer trials. Progression free survival measures the ability of a drug or device to hold tumour growth at bay at a given point in the body.

Important to know what actually kills pancreatic cancer patients – most patients die, fundamentally, from liver failure, on account of metastatic tumours. Hence we have limited our market model to include only those patients with a low metastatic burden.

What type of patients should be enrolled? Small companies seeking their first approvals should keep things simple. It makes sense to preserve as much homogeneity as possible, so we may see the trial inclusion criteria concentrate on locally advanced cases and exclude patients that have already developed visible metastases to other organs. Restrictions of this type will be reflected in the approved labelling, meaning that the product will not be actively promoted for metastatic disease. Approvals can always be broadened later by submitting additional clinical studies.

What should the comparator(s) be? We expect that the pivotal trial will have two basic arms: gemcitabine/abraxane plus Oncosil versus gemcitabine/abraxane alone. That is a highly relevant trial for the US, where gemcitabine/abraxane is in the process of becoming standard of care. Oncosil may also do another small sub-study looking at FOLFORINOX plus Oncosil versus FOLFORINOX alone – which will have clinical relevance in other markets.

What period of follow-up is appropriate? Oncosil is designed to deliver an impressively large payload of radiation: 100 Gray, over the 12 or so weeks it takes for the P^{32} to completely decay. Oncosil has said that it may follow patients for as long as 40 weeks to better characterise the two anticipated phases of tumour destruction. A period of necrotic damage is thought to follow the initial period of radiation-driven ablation.

How to allow for operator-dependency? Some trial doctors are always better than others at performing certain procedures. OncoSil™ administration is a new technique so consideration and training but be given to minimise or control for any differences between practitioners and clinical trial sites.

What future studies might be performed?

We think a number of further studies will be needed to ensure the widespread adoption of OncoSil™. All of these trials will be large studies measuring "hard" endpoints. In our modelling and valuation we have assumed that future studies are partially funded by an appropriate partner:

- **Confirm OncoSil™'s role as an adjuvant to standard chemotherapy** – quite simply a larger version of the first pivotal trial with OS as primary endpoint. This may be required in the future as a matter of course, should Oncosil use the Accelerated Approval pathway offered by the FDA.
- **Effectiveness as a single-agent in pancreatic cancer** – we believe the early clinical evidence suggests OncoSil™ may be a candidate for active monotherapy reducing tumour burden before first lines of chemotherapy are indicated. Overall survival data would also be needed to support this outcome.
- **OncoSil™ vs SBRT** – recent clinical studies (including RCTs) have demonstrated that SBRT is providing some clear benefits (overall survival and cost effectiveness) compared with more traditional external beam radiation modalities. It is not clear yet whether SBRT and OncoSil™ will be "competitors" – but it is possible because SBRT is considered in borderline-resectable cases, locally advanced and even lower burden metastatic cases – to treat the primary pancreatic tumour.

  The largest experience using SBRT for pancreatic cancer comes from Stanford University. Early studies at that centre investigating the use of a 25 Gy single fraction alone or following 45 Gy of standard fractionated chemo-radiation resulted in good local control rates of 81% and 94%, respectively, with more recent studies demonstrating acceptable gastrointestinal toxicity when specific dose constraints were implemented[25].

  A recently completed single-arm phase II multicentre study evaluated a 33 Gy dose in 5-fraction SBRT regimen following induction and consolidative single-agent gemcitabine[26]. The study demonstrated a median survival of 13.9 months, 1-year OS of 61%, low rate of late-grade 2+ toxicity (8%), and excellent quality of life scores[27].

  Although the incidence of complications has tended to decrease in larger volume centres (Johns Hopkins, Stanford), the radiation doses delivered via SBRT are considered high and it can take 5-6 weeks to transition patients through a course of therapy, as a means of managing the acute toxicities. The most serious complications include perforation/ulceration of the bowel, biliary obstruction and pain.

  We believe OncoSil™ may hold an advantage over SBRT by virtue of its single dose, which delivers 100-400 Gy in a manner that spares surrounding tissue, with potentially excellent safety. We anticipate that it will be more acceptable in the eyes of referring medical oncologists because it is less likely to complicate or delay concurrent chemotherapy.
- **First-line HCC vs sorafenib or vs SIR-Spheres** – OncoSil™ may also be assessable as a loco-regional therapy for liver cancer in its own right. A study similar in design to Sirtex's SARAH study may be contemplated (head to head with sorafenib or even SIR-Spheres)[28]. A trial like this might aim to recruit adults with advanced HCC who are not eligible for surgical resection or liver transplantation, randomising them to receive either OncoSil™ or comparator(s). An overall survival endpoint would likely require ~400 patients and 12-48 month follow-up.

[25] Koong, A. C. *et al.* (2005) *Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer*. Int J Radiat Oncol Biol Phys 63:320-323.
[26] https://clinicaltrials.gov/ct2/show/NCT01146054
[27] Herman, J. M. *et al.* (2015) *Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma* Cancer 121: 1128 – 1137.
[28] Vilgrain, V. *et al.* (2014) *Radioembolisation with yttrium-90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial.* Trials 15: 474 – 481.

Reimbursement considerations

The reimbursement case for an effective means of controlling pancreatic cancer is straightforward – if the safety and efficacy data for OncoSil™ are positive, public and private payers will support it. Our view on pricing is to assume a similar payment to that associated with current radiological standard of care (approximately US$15,000 per episode). The payer threshold in cancer can be as high as US$100,000 per quality adjusted life year (QALY).

Oncosil may have to establish its own specific coding for its device via the American Medical Association and pursue coverage decisions from CMS and private payers – Although the US Centres for Medicare and Medicaid Services (CMS) does pay for brachytherapy radiation sources, it is unlikely that these codes will be available or adequate to support OncoSil™ reimbursement. Without well-defined reimbursement coding, patients may be required to pay for the procedure out of pocket.

Relevant precedents include seed brachytherapy (prostate) and ^{90}Y microsphere products (liver) – OncoSil™ will likely qualify as a brachytherapy device because it entails penetration of the skin or surgery to insert directly into the tumour. As it is a permanent device (not removed), then its reimbursement should be separate from the implant procedure itself. That said, reimbursement practice in the US for prostate and other cancers have trended towards "bundling". Attaining specific coding, coverage and payment for OncoSil™ may protect the product-specific component of reimbursement.

SBRT health economics illustrates how it might play out for OncoSil™ – SBRT is reimbursed in most markets and believed to be more cost-effective than gemcitabine plus standard radiotherapy[29]. Recent studies compared the cost-effectiveness of four different therapies – gemcitabine, gemcitabine plus conventional radiotherapy, gemcitabine plus intensity-modulated radiation therapy (IMRT), and gemcitabine plus SBRT. The base-case cost of gemcitabine alone, gemcitabine plus SBRT, gemcitabine plus RT, and gemcitabine plus IMRT was $42,900, $56,700, $59,900 and $69,500, respectively. Overall, SBRT increased life expectancy by 0.20 QALY at an increased cost of $13,700 compared with gemcitabine alone (ICER = $69,500 per QALY). In the base-case analysis, gemcitabine plus SBRT dominated the more costly and less effective options.

Pancreatic brachytherapy unlikely to suffer technological shift, as was the case for prostate brachytherapy – brachytherapy (radioactive "seed" implants) is a safe and effective initial treatment for prostate cancer. Numerous studies with up to 12 years of follow-up have demonstrated excellent disease-specific and overall survival for patients with prostate cancer treated with brachytherapy, particularly those at low risk. Brachytherapy fell out of favour with urologists following the advent of robotic laparoscopy treatment for radical prostatectomy in the early 2000s. For radiation oncologists, brachytherapy was considered time-consuming and resource-intensive, requiring the physician to be present for the entire procedure which includes general anaesthesia. Another reason for brachytherapy's decline was reimbursement-related: the cost of the therapy came to be "bundled" with related services.

It is therefore important that Oncosil develops unique codes for its product, and carefully positions the therapy to succeed under value-based payment regimes.

[29] Murphy, J. D. *et al*. (2012) *Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer*. Cancer 118, 1119–1129.

Manufacturing and quality considerations

OncoSil™ microparticles are manufactured from silicon (Si) and phosphorous following a five-step procedure – extremely highly phosphorous-doped Si microparticles are engineered from ultrapure polycrystalline Si using foundry techniques and water atomisation. After size classification to a particle size of ~30 microns, these particles are acid cleaned and stain etched. The powder then undergoes irradiation in a nuclear reactor to create the phosphorous isotope P^{32}. This isotope is an excellent choice for brachytherapy due to its beta-emitting properties and moderate half-life. Its energy emission has a maximum tissue range of ~8 mm and a half-life of about a fortnight (343 hours). OncoSil™ doses are expected to be manufactured on demand – packaged and shipped in lead-lined containers for reconstitution and delivery at the hospital.

November 2014, Oncosil re-validated its manufacturing and quality systems in conjunction with Eckert & Ziegler, a German manufacturer – the OncoSil™ manufacturing process and distribution requirements bear some similarity to that of Sirtex's Y^{91}-loaded resin microspheres. Historically, Sirtex has maintained gross margins of ~84% and we expect that Oncosil could achieve similar gross profitability, at scale.

In March 2015, Oncosil announced ISO 13485 certification for the design, development and control of manufacturing – this was a key requirement for Oncosil's goal of attaining CE Mark, which enables marketing clearance in the European Union. The CE Mark designation will confirm, in an internationally recognised way, the safety and functional utility of the product. By that we mean quality, safety and consistency of manufactured product, and at the product level, predictable and reproducible performance – in terms of OncoSil™'s basic properties as a radiation source.

Financials

Table 7: Revenue model – product sales in pancreatic cancer

OncoSil - Pancreatic Cancer Market Model	FY16	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30
USA															
Incident population	48,960	49,450	49,944	50,444	50,948	51,457	51,972	52,492	53,017	53,547	54,082	54,623	55,169	55,721	56,278
Eligible population	39,535	39,931	40,330	40,733	41,140	41,552	41,967	42,387	42,811	43,239	43,671	44,108	44,549	44,995	45,445
Locally advanced	18,582	18,767	18,955	19,145	19,336	19,529	19,725	19,922	20,121	20,322	20,526	20,731	20,938	21,148	21,359
Metastatic	20,954	21,163	21,375	21,589	21,804	22,023	22,243	22,465	22,690	22,917	23,146	23,377	23,611	23,847	24,086
Pts seeking treatment	**20,831**	**21,039**	**21,250**	**21,462**	**21,677**	**21,894**	**22,113**	**22,334**	**22,557**	**22,783**	**23,010**	**23,241**	**23,473**	**23,708**	**23,945**
ASP (US$ per dose)	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000
Units				300	450	1,125	2,250	3,375	4,219	5,063	5,974	6,870	8,267	10,500	14,535
' dose grow th					50%	150%	100%	50%	25%	20%	18%	15%	20%	27%	38%
Implied penetration in eleigible popn				*0.7%*	*1.1%*	*2.7%*	*5.4%*	*8.0%*	*9.9%*	*11.7%*	*13.7%*	*15.6%*	*18.6%*	*23.3%*	*32.0%*
Net sales (US$m)	**-**	**-**	**-**	**4.5**	**6.8**	**16.9**	**33.8**	**50.6**	**63.3**	**75.9**	**89.6**	**103.0**	**124.0**	**157.5**	**218.0**
Net sales (A$m)	**-**	**-**	**-**	**5.6**	**8.4**	**21.1**	**42.2**	**63.3**	**79.1**	**94.9**	**112.0**	**128.8**	**155.0**	**196.9**	**272.5**
5EU															
Incident population	67,761	68,439	69,123	69,814	70,512	71,217	71,930	72,649	73,375	74,109	74,850	75,599	76,355	77,118	77,889
Eligible population	54,717	55,264	55,817	56,375	56,939	57,508	58,083	58,664	59,251	59,843	60,442	61,046	61,656	62,273	62,896
Locally advanced	25,717	25,974	26,234	26,496	26,761	27,029	27,299	27,572	27,848	28,126	28,408	28,692	28,979	29,268	29,561
Metastatic	29,000	29,290	29,583	29,879	30,178	30,479	30,784	31,092	31,403	31,717	32,034	32,354	32,678	33,005	33,335
Pts seeking treatment	**28,830**	**29,119**	**29,410**	**29,704**	**30,001**	**30,301**	**30,604**	**30,910**	**31,219**	**31,531**	**31,847**	**32,165**	**32,487**	**32,812**	**33,140**
ASP (EUR per dose)	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Units	100	130	195	293	439	878	1,141	1,483	2,002	2,503	3,003	3,604	4,144	4,766	5,481
' dose grow th		30%	50%	50%	50%	100%	30%	30%	35%	25%	20%	20%	15%	15%	15%
Implied penetration in eleigible popn	*0.2%*	*0.2%*	*0.3%*	*0.5%*	*0.8%*	*1.5%*	*2.0%*	*2.5%*	*3.4%*	*4.2%*	*5.0%*	*5.9%*	*6.7%*	*7.7%*	*8.7%*
Net sales (EURm)	**1.0**	**1.3**	**2.0**	**2.9**	**4.4**	**8.8**	**11.4**	**14.8**	**20.0**	**25.0**	**30.0**	**36.0**	**41.4**	**47.7**	**54.8**
Net sales (A$m)	**1.4**	**1.9**	**2.8**	**4.2**	**6.3**	**12.5**	**16.3**	**21.2**	**28.6**	**35.8**	**42.9**	**51.5**	**59.2**	**68.1**	**78.3**
ROW															
Incident population	100,000	101,000	102,010	103,030	104,060	105,101	106,152	107,214	108,286	109,369	110,462	111,567	112,683	113,809	114,947
Eligible population	80,750	81,558	82,373	83,197	84,029	84,869	85,718	86,575	87,441	88,315	89,198	90,090	90,991	91,901	92,820
Locally advanced	37,953	38,332	38,715	39,102	39,494	39,888	40,287	40,690	41,097	41,508	41,923	42,342	42,766	43,193	43,625
Metastatic	42,798	43,225	43,658	44,094	44,535	44,981	45,430	45,885	46,344	46,807	47,275	47,748	48,225	48,708	49,195
Pts seeking treatment	**42,547**	**42,973**	**43,402**	**43,836**	**44,275**	**44,718**	**45,165**	**45,616**	**46,072**	**46,533**	**46,999**	**47,469**	**47,943**	**48,423**	**48,907**
ASP (A$ per dose)	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500
Units		25	50	62.5	93.75	187.5	234	293	366	458	572	715	894	1,118	1,397
' dose grow th			100%	25%	50%	100%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Implied penetration in eleigible popn	*0.0%*	*0.0%*	*0.1%*	*0.1%*	*0.1%*	*0.2%*	*0.3%*	*0.3%*	*0.4%*	*0.5%*	*0.6%*	*0.8%*	*1.0%*	*1.2%*	*1.5%*
Net sales (A$m)	**-**	**0.2**	**0.3**	**0.4**	**0.6**	**1.2**	**1.5**	**1.9**	**2.4**	**3.0**	**3.7**	**4.6**	**5.8**	**7.3**	**9.1**
Total Dose Sales	100	155	245	655	983	2,190	3,625	5,151	6,587	8,023	9,549	11,189	13,305	16,383	21,413
Global gross revenue ($Am)	**1.4**	**2.0**	**3.1**	**10.2**	**15.3**	**34.8**	**60.0**	**86.4**	**110.1**	**133.6**	**158.6**	**184.9**	**220.0**	**272.2**	**359.9**

Source: WHTM Research

Table 8: Revenue model – product sales in hepatocellular carcinoma

	FY16	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30
USA															
Incident population	35,660	36,017	36,377	36,741	37,108	37,479	37,854	38,232	38,615	39,001	39,391	39,785	40,183	40,584	40,990
Intermediate to advanced	15,156	15,307	15,460	15,615	15,771	15,929	16,088	16,249	16,411	16,575	16,741	16,909	17,078	17,248	17,421
Palliative treatment	12,882	13,011	13,141	13,273	13,405	13,539	13,675	13,811	13,950	14,089	14,230	14,372	14,516	14,661	14,808
Salvage therapy	1,819	1,837	1,855	1,874	1,893	1,911	1,931	1,950	1,969	1,989	2,009	2,029	2,049	2,070	2,091
Pts seeking treatment	**9,359**	**9,452**	**9,547**	**9,642**	**9,739**	**9,836**	**9,934**	**10,034**	**10,134**	**10,235**	**10,338**	**10,441**	**10,545**	**10,651**	**10,757**
ASP (US$ per dose)	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000
Units				50	100	175	525	656	788	945	1,115	1,282	1,475	1,696	1,950
' dose grow th					100%	75%	200%	25%	20%	20%	18%	15%	15%	15%	15%
Implied penetration in eleigible popn				*0.3%*	*0.6%*	*1.1%*	*3.3%*	*4.0%*	*4.8%*	*5.7%*	*6.7%*	*7.6%*	*8.6%*	*9.8%*	*11.2%*
Net sales (US$m)	**-**	**-**	**-**	**0.8**	**1.5**	**2.6**	**7.9**	**9.8**	**11.8**	**14.2**	**16.7**	**19.2**	**22.1**	**25.4**	**29.3**
Net sales (A$m)	**-**	**-**	**-**	**0.9**	**1.9**	**3.3**	**9.8**	**12.3**	**14.8**	**17.7**	**20.9**	**24.0**	**27.7**	**31.8**	**36.6**
5EU															
Incident population	49,924	50,423	50,927	51,437	51,951	52,471	52,995	53,525	54,061	54,601	55,147	55,699	56,256	56,818	57,386
Intermediate to advanced	21,218	21,430	21,644	21,861	22,079	22,300	22,523	22,748	22,976	23,205	23,438	23,672	23,909	24,148	24,389
Palliative treatment	16,974	17,144	17,315	17,488	17,663	17,840	18,018	18,199	18,381	18,564	18,750	18,938	19,127	19,318	19,511
Salvage therapy	2,546	2,572	2,597	2,623	2,650	2,676	2,703	2,730	2,757	2,785	2,813	2,841	2,869	2,898	2,927
Pts seeking treatment	**12,391**	**12,515**	**12,640**	**12,767**	**12,894**	**13,023**	**13,153**	**13,285**	**13,418**	**13,552**	**13,688**	**13,824**	**13,963**	**14,102**	**14,243**
ASP (EUR per dose)	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000	8,000
Units	25	50	100	150	240	360	540	810	1,215	1,458	1,720	1,979	1,979	1,979	1,979
' dose grow th		100%	100%	50%	60%	50%	50%	50%	50%	20%	18%	15%	15%	15%	15%
Implied penetration in eleigible popn	*0.1%*	*0.2%*	*0.5%*	*0.7%*	*1.1%*	*1.6%*	*2.4%*	*3.6%*	*5.3%*	*6.3%*	*7.3%*	*8.4%*	*8.3%*	*8.2%*	*8.1%*
Net sales (EURm)	**0.2**	**0.4**	**0.8**	**1.2**	**1.9**	**2.9**	**4.3**	**6.5**	**9.7**	**11.7**	**13.8**	**15.8**	**15.8**	**15.8**	**15.8**
Net sales (A$m)	**0.3**	**0.6**	**1.1**	**1.7**	**2.7**	**4.1**	**6.2**	**9.3**	**13.9**	**16.7**	**19.7**	**22.6**	**22.6**	**22.6**	**22.6**
APAC															
Incident population	1,500	1,515	1,530	1,545	1,561	1,577	1,592	1,608	1,624	1,641	1,657	1,674	1,690	1,707	1,724
Intermediate to advanced	638	644	650	657	663	670	677	683	690	697	704	711	718	726	733
Palliative treatment	510	515	520	525	531	536	541	547	552	558	563	569	575	580	586
Salvage therapy	77	77	78	79	80	80	81	82	83	84	85	85	86	87	88
Pts seeking treatment	**372**	**376**	**380**	**384**	**387**	**391**	**395**	**399**	**403**	**407**	**411**	**415**	**420**	**424**	**428**
ASP (A$ per dose)	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Units			20	40	80	100	125	153	180	198	208	218	229	236	238
' dose grow th			100%	100%	100%	25%	25%	22%	18%	10%	5%	5%	5%	3%	1%
Implied penetration in eleigible popn	*0.0%*	*0.0%*	*3.1%*	*6.1%*	*12.1%*	*14.9%*	*18.5%*	*22.3%*	*26.1%*	*28.4%*	*29.5%*	*30.7%*	*31.9%*	*32.5%*	*32.5%*
Net sales (A$m)	**-**	**-**	**0.1**	**0.2**	**0.4**	**0.5**	**0.6**	**0.8**	**0.9**	**1.0**	**1.0**	**1.1**	**1.1**	**1.2**	**1.2**
Total Dose Sales	25	50	120	240	420	635	1,190	1,619	2,182	2,601	3,043	3,479	3,682	3,910	4,167
Global gross revenue ($Am)	**0.3**	**0.6**	**1.2**	**2.9**	**5.0**	**7.9**	**16.6**	**22.3**	**29.6**	**35.4**	**41.6**	**47.7**	**51.4**	**55.6**	**60.4**

Source: WHTM Research

Table 9: Revenue, earnings and cash flow model

INCOME STATEMENT															
REVENUE	FY16	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30
OncoSil™ net sales	1.4	2.0	3.1	10.2	15.3	17.4	30.0	43.2	55.0	66.8	79.3	92.5	110.0	136.1	180.0
COGS	0.6	0.8	1.0	2.0	2.8	3.2	5.2	7.0	8.6	10.3	12.2	14.2	16.8	20.7	27.3
Gross profit	**0.8**	**1.2**	**2.1**	**8.2**	**12.5**	**14.2**	**24.9**	**36.2**	**46.5**	**56.5**	**67.1**	**78.3**	**93.2**	**115.4**	**152.7**
- gross margin	*58%*	*58%*	*67%*	*80%*	*81%*	*82%*	*83%*	*84%*	*84%*	*85%*	*85%*	*85%*	*85%*	*85%*	*85%*
Other income	0.5	3.6	3.8	3.4	3.7	4.0	4.3	3.4	2.0	2.0	2.0	2.0	2.0	2.0	2.0
R&D	(4.2)	(11.0)	(8.2)	(8.8)	(9.5)	(10.3)	(11.5)	(12.9)	(14.5)	(16.3)	(18.3)	(20.6)	(23.1)	(26.0)	(29.2)
Sub-royalties to PVA	(0.1)	(0.2)	(0.2)	(0.8)	(1.2)	(1.4)	(2.4)	(3.5)	(4.4)	(5.3)	(6.3)	-	-	-	-
SG&A	(3.2)	(3.7)	(6.1)	(7.2)	(4.2)	(4.4)	(5.4)	(6.4)	(7.4)	(8.3)	(9.3)	(10.4)	(11.8)	(13.8)	(17.2)
EBITDA	**(6.1)**	**(10.1)**	**(8.6)**	**(5.2)**	**1.2**	**2.1**	**9.9**	**16.8**	**22.2**	**28.5**	**35.1**	**49.3**	**60.3**	**77.6**	**108.3**
- EBITDA margin						*12%*	*33%*	*39%*	*40%*	*43%*	*44%*	*53%*	*55%*	*57%*	*60%*
EBIT	**(6.2)**	**(10.2)**	**(8.7)**	**(5.3)**	**1.2**	**2.0**	**9.9**	**16.7**	22.1	28.4	35.0	49.2	60.2	77.5	108.2
Net interest	0.1	0.3	0.1	0.1	0.1	0.1	0.1	0.4	0.7	1.0	1.3	1.3	1.3	1.2	1.2
Tax	-	-	-	-	-	-	-	-	(5.3)	(7.1)	(8.7)	(12.1)	(14.8)	(18.9)	(26.3)
NPAT	**(6.1)**	**(9.9)**	**(8.5)**	**(5.2)**	**1.2**	**2.1**	**10.0**	**17.1**	**17.4**	**22.4**	**27.6**	**38.4**	**46.7**	**59.8**	**83.1**
EPS (cps)	**(1.6)**	**(2.2)**	**(1.9)**	**(1.1)**	**0.3**	**0.5**	**2.2**	**3.7**	**3.8**	**4.9**	**6.1**	**8.4**	**10.3**	**13.1**	**18.3**

BALANCE SHEET															
	FY16	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30
ASSETS	**18.9**	**9.1**	**10.6**	**6.2**	**7.8**	**10.1**	**21.1**	**39.0**	**57.4**	**80.7**	**81.7**	**82.8**	**84.4**	**86.1**	**89.8**
Cash	18.4	7.5	8.9	3.0	3.5	5.3	13.9	29.8	46.0	67.1	65.8	64.5	62.4	60.2	55.7
LIABILITIES	**0.6**	**0.6**	**10.7**	**10.3**	**9.8**	**9.0**	**9.0**	**8.8**	**8.8**	**8.7**	**8.7**	**8.7**	**9.4**	**11.1**	**14.8**
EQUITY	**18.4**	**8.5**	**- 0.0**	**- 4.2**	**- 2.0**	**1.2**	**12.1**	**30.2**	**48.7**	**72.0**	**73.0**	**74.0**	**75.0**	**75.0**	**75.0**
Accumulated profits/(losses)	(24.8)	(34.7)	(43.2)	(47.3)	(45.1)	(42.0)	(31.0)	(13.0)	5.5	28.9	29.9	30.9	31.9	31.9	31.9
Equity	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3	41.3

CASH FLOW															
	FY16	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30
Operating cash	(6.0)	(10.7)	1.6	(5.7)	0.8	2.0	8.8	16.1	16.4	21.4	26.5	37.3	44.8	57.9	78.8
Investment	(0.4)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)
Financing	17.5	-	-	-	-	-	-	-	-	-					
Net cash flow	**11.1**	**(10.9)**	**1.4**	**(5.9)**	**0.6**	**1.8**	**8.6**	**15.9**	**16.2**	**21.2**	**26.3**	**37.1**	**44.6**	**57.7**	**78.6**

Source: WHTM Research

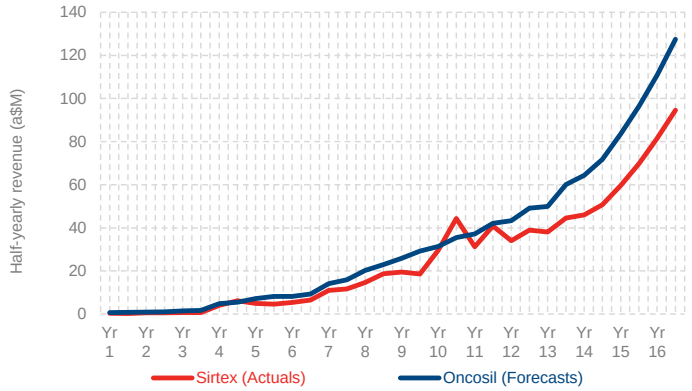
Financials

Assumptions and further notes

Revenue model – product sales

- OncoSil™ sales as per the market models described in Tables 7-9. We see our average selling price assumptions as conservative, compared against SIR-Spheres, which is currently achieving US$18,000 per dose in treating metastatic colorectal cancer.
- The epidemiological model for pancreatic excludes resectable disease (15%) and non-adenocarcinomas (5%). We assume that two-thirds of locally advanced cases may seek treatment. We model a lower access rate in metastatic disease, given that the product should be best suited to low tumour burden cases. The epidemiological model for HCC is similar to that we model for SIR-Spheres in that setting. We define the eligible population as two-thirds of the palliative market and ~40% of the salvage market. It is a materially smaller market for OncoSil™, overall, compared with pancreatic cancer.
- We have assumed an initial direct launch in Europe, which may transition into a partnering arrangement in FY19-20. Innumerable commercial arrangements are possible but the one we have modelled has: a) the partner and not Oncosil sharing the costs of sales representatives; b) Oncosil retaining control over medical affairs, market education and clinical site training; and c) an exclusive agency under which Oncosil receives 50% of end-market net sales. We extend the agency model to our forecasts for the US market.

Figure 8: Our long-term revenue forecasts compare reasonably well with Sirtex's historical performance



Source: WHTM Research

Earnings and cash flow

- Gross margin – a three-year ramp towards 85% gross margin, maintained thereafter.
- SG&A – although OncoSil's cost structure is years from developing, we think that a long-term 50-55% EBITDA margin can be achieved and sustained given the very high gross profit starting point.
- R&D – the US IDE clinical trial campaign should cost $7-10m. We expect R&D expenses to moderate from FY17 onwards. In the long term we grow annual R&D expense by ~6% which represents 16-25% of net sales. This is in line with mature medical device companies.
- Under a December 2012 licence agreement, amended and restated in 2013, Oncosil Medical is liable to pay pSiMedica (subsidiary of pSiVida Corp or PVA) an 8% sales-based royalty, 20% of any sublicensing consideration and milestone payments based on aggregate product sales. Oncosil Medical is also obligated to pay an annual licence maintenance fee of $100K, creditable during each ensuing 12-month period against reimbursable patent maintenance costs and sales-based royalties[30].

[30] Source: pSiVida Form 10-K Annual Report 2013.

Board and management

Board

Dr Roger Aston, Chairman – Dr Aston has had extensive experience on boards of many pharmaceutical companies, and has been CEO of Pitney Pharmaceuticals, PSIMEDICA, PSIONCOLOGY, Peptech and Cambridge Antibody Technology. In 2001, Dr Aston co-founded pSivida. He served as the Chief Executive Officer of Hospira Australia, and as Chief Executive Officer of Mayne Pharma Group until February 15, 2012. During his career, Dr Aston has been closely involved in start-up companies and major pharmaceutical companies. Aspects of his experience include FDA and EU product registration, clinical trials, global licensing agreements, fundraising through private placements, and a network of contacts within the pharmaceutical, banking and stock broking sectors.

Daniel Kenny, Managing Director – Mr Kenny joined Oncosil in January 2015 with almost 30 years' experience in the global pharmaceutical and medical device industry. He is an accomplished and proven biopharmaceutical business leader and in his career he has developed and successfully driven business with industry leaders such as Roche, Allergan and Baxter working in Australia, EMEA and the US. Prior to joining Oncosil, Mr Kenny held the position of Chief Commercial Officer at ABIVAX, a Paris-based global biopharmaceutical company specialising in the development of novel vaccines and anti-virals. At Baxter he served as Global Franchise Head Vaccines overseeing all Franchise Operations. Before this role, he served as Vice President Baxter BioScience, EMEA, with responsibility for all marketing and key business programs in support of regional sales exceeding $1.9bn.

Martin Rogers, Non-executive Director – Mr Rogers is a successful start-up investor and company director. He has Chemical Engineering and Science degrees and has a depth of experience in incubating companies and publicly listed organisations. He has experience in all aspects of financial, strategic and operational management and has helped raise more than $100m equity. Mr Rogers has been both an investor and senior executive in a private funded advisory business in the science and biotechnology sectors, where he was instrumental in significantly increasing the value of those investments. Mr Rogers also holds a number of not-for-profit roles, and is Chairman of Rhinomed and non-executive director of Cellmid.

Management

Daniel Kenny, CEO – as above.

Dr Ash Soman, Chief Medical Officer – Dr Soman is a highly experienced medical professional and pharmaceutical industry executive with more than 24 years' experience. His previous roles include Country Medical Director, Australia for major bio-pharmaceutical company AstraZeneca, from 2012-14, where he managed a team of 30 employees spanning medical affairs, medical information and publications, compliance and patient safety. Prior to that he was Medical Director – Cardiovascular & Diabetes for AstraZeneca Australia, from 2009-12. Dr Soman has also previously held roles with Sanofi-aventis Australia-New Zealand, from 2006-09, and Roche Products in the UK, from 2004-06. He commenced his career as a practising hospital clinician in 1991 with the UK National Health Service.

Natalie Ruffles, Vice President Clinical Operations – Ms Ruffles has a strong depth of experience and expertise in running clinical trials for medical devices and pharmaceutical investigational products, over a period of 10 years. Ms Ruffles most recently worked for leading US medical device company Medtronic, where she was responsible for managing its clinical programs in Australia/New Zealand. Prior to this, she worked for a number of global contract research organisations (CROs) in monitoring, project management and business development roles.

Aoifa Brogan, Vice President Regulatory Affairs – Mr Brogan has almost 15 years' professional experience in the medical device industry. Having obtained a Biomedical Engineering degree, she began her career as a Research and Development Engineer with Medtronic Ireland. In May 2005 she was internally recruited to the Regulatory Affairs department, and subsequently took up regulatory positions in Medtronic Danvers (US) and Medtronic Australasia. In February 2010 Ms Brogan joined a Sydney-based CRO to establish the regulatory affairs department and to provide strategic regulatory advice to clients performing clinical trials and/or seeking commercial approval in Australia.

David James, Vice President Manufacturing and Operations – Mr James has 25 years' experience in the pharmaceutical, radio-pharmaceutical, medical device and veterinary medicines. He was Global Operations Manager for Sirtex Medical during its formative years (2001-06).

Oncosil Medical Limited (OSL)

BUSINESS DESCRIPTION

Oncosil Medical Limited (OSL) is developing a novel form of brachytherapy for the treatment of pancreatic and liver cancers. OncoSil™ provides a means of irradiating tumours from the inside, using microparticles impregnated with the radioactive isotope Phosphorus-32. OncoSil™ is expected to be granted CE Mark this year and be the subject of a large clinical trial in the US next year. We estimate a US$250m sales opportunity in the major pancreatic cancer markets.

INVESTMENT THESIS

OncoSil™ is an attractive product concept on account of its "single treatment" nature and dose intensity. We think the product deserves "accelerated review" status with the FDA and will find good adoption by interventional radiologists, if approved.

REVENUE DRIVERS

- Pricing and reimbursement
- Market penetration (new clinical centres/hospitals, physician acceptance)
- New markets (geographical, clinical indications)

BALANCE SHEET

- As at the 1HFY15 result, Oncosil had ~$7m in cash and no debt

MARGIN DRIVERS

- Gross margins sustainable at 80% or better
- Although SG&A structure is yet to evolve WHTMe long-term rates of ~40-50% achievable
- Reimbursement

BOARD

- Roger Aston (Chairman)
- Daniel Kenny (Managing Director)
- Martin Rogers (Non-executive Director)

KEY ISSUES/CATALYSTS

- CE Marking and European marketing
- Clinical trial design and FDA approvals

MANAGEMENT

- Daniel Kenny (CEO)
- Ashish Soman (CMO)
- Natalie Ruffles (VP Clinical)
- Aoifa Brogan (VP Regulatory)
- David James (VP Manufacturing)

RISK TO VIEW

- Outlook depends on quality of evidence flowing from clinical trials
- Regulatory risks including manufacturing and quality
- Product safety
- Competitive risks in a busy oncology technology market

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Disclosures and disclaimers

Recommendation structure and other definitions

Definitions at http://www.wilsonhtm.com.au/Disclosures

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Disclosure of interest. Oncosil Medical Limited

The Directors of Wilson HTM Ltd advise that at the date of this report they and their associates have relevant interests in Oncosil Medical Ltd. They also advise that Wilson HTM Ltd and Wilson HTM Corporate Finance Ltd A.B.N. 65 057 547 323 and their associates have received and may receive commissions or fees from Oncosil Medical Ltd in relation to advice or dealings in securities. Some or all of Wilson HTM Ltd authorised representatives may be remunerated wholly or partly by way of commission.

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