EDISON

Telix Pharmaceuticals

Initiation of coverage

Targeted radiation to image and treat cancer

Pharma & biotech

Telix has assembled a portfolio of promising molecularly targeted radiation (MTR) therapeutic and imaging products for three different cancers. Each product has been validated by clinical studies or compassionate use in patients, thus reducing development risk. Telix is positioned to add significant value, such as by refining the products or developing them as a combination therapy. Preparations for a confirmatory Phase III study for kidney cancer imaging agent TLX250-CDx and for multiple Phase I/II studies of other agents are underway. It has begun commercialisation of an investigational prostate cancer imaging kit in the US, and plans are being developed for a short pivotal study to allow full approval. Our initial valuation is A$303m or A$1.39 per share.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/17	0.4	(6.4)	(5.0)	0.0	N/A	N/A
12/18e	5.0	(12.7)	(6.1)	0.0	N/A	N/A
12/19e	8.4	(17.7)	(8.1)	0.0	N/A	N/A
12/20e	6.6	(15.8)	(7.3)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding exceptionals and share-based payments.

Assembled a portfolio of advanced products

Telix's MTR products comprise a radioactive isotope attached to either an antibody or small molecule that targets delivery to tumour cells in kidney, prostate or brain cancers (TLX250, TLX591 and TLX101, respectively). The companion diagnostic TLX250-CDx previously demonstrated high sensitivity and specificity for imaging clear cell renal cell carcinoma, the most common and aggressive form of kidney cancer, in a Phase III study. The product has been enhanced and the confirmatory ZIRCON Phase III will begin in Q418 on the completion of a short bridging study.

Well-funded to achieve milestones

Development of some portfolio products stalled under previous ownership due to lack of funds or other roadblocks. Telix is well funded to progress key projects to milestones. Management has extensive experience developing radio-therapeutics.

Refining products and revising strategy to add value

Telix has modified a number of the acquired products to enhance their properties, and has revised and updated the development strategies to account for recent market developments, including plans for combination therapy with immune checkpoint inhibitors. Modifications to individual products include changing to a different radionuclide that generates sharper images or by tweaking the targeting antibody to improve pharmacodynamics and ease of manufacture.

Valuation: A$303m or A$1.39/share

We value Telix at A$303m or A$1.39/share based on an rNPV using a 12.5% discount rate and assuming Telix acquires Atlab for 20.5m shares (US$10m) in Q318. We include milestones and royalties for TLX250, and TLX591, plus profits from commercialisation of TLX250-CDx, TLX591-CDx and TLX101.

20 August 2018

Price	**A$0.79**
Market cap	**A$156m**
	US$0.76/A$
Net cash (A$m) at 30 June 2017	42.0
Shares in issue	197.4m
Free float	58%
Code	TLX
Primary exchange	ASX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	17.0	12.1	N/A
Rel (local)	14.5	8.1	N/A
52-week high/low	A$0.79		A$0.48

Business description

Telix Pharmaceuticals is a Melbourne-headquartered global biopharmaceutical company focused on the development of diagnostic and therapeutic products based on targeted radiopharmaceuticals or molecularly targeted radiation.

Next events

Phase III submission for ZIRCON study	Q318
Launch of IPAX-1 brain cancer study	Q318
Commercial/distributor roadmap for prostate imaging kit	Q318

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Edison profile page

Telix Pharmaceuticals is a research client of Edison Investment Research Limited

Investment summary

Company description: Molecularly targeted radiation

Telix is a biotechnology company that is developing molecularly targeted pharmaceutical products for imaging and treating a range of cancers. It is developing TLX250-CDx and TLX250 for imaging and treating the kidney cancer known as clear cell renal cell carcinoma (ccRCC); TLX591-CDx and TLX591 for imaging and treating prostate cancer; and TLX101-CDx and TLX101 for imaging and treating brain cancer (TLX101-CDx will be used for studying the pharmacology of TLX101 but will not be developed for clinical use). TLX250-CDx, which now uses the ^{89}Zr radionuclide that produces sharper images, is in a bridging study ahead of the confirmatory ZIRCON Phase III trial expected to commence in Q418. The TLX101 therapeutic agent is expected to enter a Phase I study in the current quarter. A drug master file (DMF) for the TLX591 prostate cancer imaging kit has passed review by the US FDA. TLX591-CDx is now available for use in clinical trials, and a commercial launch as an investigational imaging tool is expected in Q318.

Valuation: A$303m or A$1.39 per share

Our initial valuation of Telix is A$303m or A$1.39 per share, which includes our estimates of the future milestone payments and royalty streams for TLX250 and TLX591, plus profits from commercialisation of TLX250-CDx, TLX591-CDx and TLX101. Our rNPV calculation is based on the assumptions discussed below, such as target population, market uptake, pricing, R&D costs, market exclusivity expiry and calculated peak sales. Telix's strategy is to self-commercialise TLX250-CDx, TLX591-CDx and TLX101 due to the compact market structure for these products. For TLX591 and TLX250 its strategy is to seek a marketing partner to promote the products into the more dispersed urology market. We assume the trigger for a licensing deal could be positive Phase I/II or Phase II data for the TLX250 and TLX591 therapeutic agents.

Financials: Funded until 2020

Telix reported an operating loss of A$6.4m in 2017, its first year of operation. Expenses associated with R&D projects were A$3.0m, personnel expenses were A$1.3m and administration and consulting costs totalled A$2.3m. Our total operating loss estimates for 2018, 2019 and 2020 grow to A$13.0m, A$17.9m and A$15.8m, respectively, mainly due to increased R&D expenditure as Telix progresses its clinical trial programme, partly offset by the Australian government's R&D rebate scheme. Telix had A$42.0m cash and equivalents at 30 June 2018 and is funded into 2020. However, we estimate that it may need additional funding in 2020 (we model of A$4m of indicative debt) if it does not enter a licensing transaction before 2021.

Sensitivities: Typical biotech risks apply

Telix is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that TLX250 and TLX591 will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. While Telix is commencing commercialisation of TLX591-CDx, it is still mainly a mid-stage drug developer, therefore in the foreseeable future most value creation will depend on successful R&D progress and any potential partnering activities. If the FDA requires Telix to conduct a prospective clinical study of TLX591-CDx rather than a blinded review of existing scans, it could delay filing for full marketing approval by one to two years. We model use of TLX591-CDx as a second-line test in prostate cancer patients following biochemical relapse when metastases cannot be detected by CT or MRI scans, but if it becomes a first-line test in these patients, the addressable market could be significantly larger.

Company description: Using radiation to target cancer

Telix Pharmaceuticals is based in Melbourne, Australia and focuses on the development of MTR products (also referred to as targeted radiopharmaceuticals) to image and treat cancer. The company was incorporated in January 2017 and listed on the Australian Stock Exchange (ASX) in November 2017 after raising A$50m (before costs) in an IPO. The company's founders, Christian Behrenbruch (CEO) and Andreas Kluge (CMO), are experienced executives and drug developers in the field of radiopharmaceuticals. The company's portfolio consists of a pipeline of in-licensed and acquired products as well as company-originated intellectual property (Exhibit 1). The key transactions are summarised below.

In January 2017 the company in-licensed the rights to the underlying antibody technology behind the TLX250 programme from Wilex (Deutsche Börse ETR: WL6).

In July 2017 the company inlicensed from Abzena PLC (LON: ABZA) several patents that form the basis of the TLX591 portfolio. Telix is working with Abzena on a number of protein engineering enhancements to its programmes.

Telix has a collaborative agreement with the privately held French biotech Atlab Pharma SAS around clinical data and manufacturing process development for TLX591. Telix is likely to exercise its option to acquire Atlab for ~US$10m in cash or shares (we model 20.5m shares). Atlab licensed the huJ591 anti-PSMA antibody technology from Cornell and has rights to several patents that relate to the combination use of TLX591and other prostate cancer drugs including anti-androgen drugs.

In October 2017 Telix acquired the privately held German company Therapeia, obtaining the background technology to TLX101.

Exhibit 1 summarises the key features of the six products in the company's portfolio.

Exhibit 1: Telix development programmes

Product	Cancer	Molecular target, targeting agent, isotope	Stage	Notes
TLX250-CDx (imaging)	Kidney cancer (ccRCC)	CA-IX mAb ^{89}Zr	Phase III bridging study underway; ZIRCON Phase III expected to commence Q418	Isotope changed from ^{124}I to ^{89}Zr to improve image quality.
TLX250 (therapeutic)	Kidney cancer (ccRCC)	CA-IX mAb ^{177}Lu	US Phase II planned	Three Phase II checkpoint inhibitor combo studies planned. Targeting US/Australia IND filings Q418.
TLX591-CDx (imaging)	Prostate cancer	PSMA small molecule ^{68}Ga	DMF passed FDA review	First commercial revenues from US sales as an investigational imaging test expected in H218.
TLX591 (therapeutic)	Prostate cancer	PSMA mAb ^{177}Lu	Phase I/II planned	Drug product in manufacturing for Q119 start.
TLX101-CDx (imaging)	Brain cancer (GBM)	LAT-1 small molecule ^{124}I	Research use only	Use of TLX101-CDx will be limited to studying the pharmacology of TLX101.
TLX101 (therapeutic)	Brain cancer (GBM)	LAT-1 small molecule ^{131}I	IPAX-1 Phase I/II pending	Phase I/II IMPD* to be filed in EU shortly.

Source: Edison Investment Research, Telix. Note: *IMPD= investigational medicinal product dossier; ccRCC= clear cell renal cell carcinoma; GBM= glioblastoma.

MTR to image and treat cancer

MTR products selectively deliver radiation to cells with molecular markers or targets that are over-expressed in cancer. The radiation can be used to facilitate imaging a tumour to diagnose or stage a patient, or may be a therapeutic dose to treat the cancer. MTR products enable medical imaging, for example positron emission tomography (PET), to determine the true extent of disease and can also evaluate whether a treatment target is present. Exhibit 2 illustrates how MTR works.

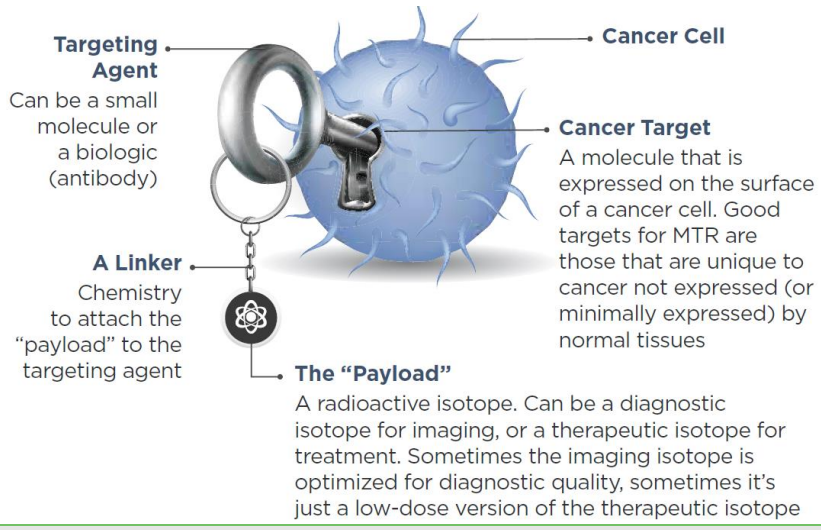
The MTR products in use or in development use a range different of radioactive isotopes and targeting agents to address target molecular targets in cancer cells. For example, the most widely

used PET imaging agent, ^{18}F -fludeoxyglucose (FDG), which is widely used for detecting and monitoring cancer, relies on the fact that many tumours are metabolically active with a high glucose uptake. However, FDG PET is not very useful for imaging cancers such as prostate cancer that are not very metabolically active, or for organs where the signal from a tumour can be obscured by labelled FDG excreted in the urine.

Telix's MTR imaging agents target molecular markers that are overexpressed on particular cancers. Their specificity for cancer cells makes them particularly useful for identifying small metastases that cannot be detected by other methods and for monitoring patients for recurrence or metastatic spread of the disease. In the case of TLX250-CDx, a key intended application is for distinguishing between benign lumps and dangerous kidney cancers.

Telix's MTR therapeutics target delivery of radioactive payload to the tumour to kill cancer cells.

Exhibit 2: How MTR works



Source: Telix prospectus

Novartis's US$3.9bn acquisition of Lutathera shows that big pharma is keenly interested in MTR

In September 2017 the EU approved an MTR therapeutic product known as ^{177}Lu dotatate, or Lutathera, for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs), a rare form of cancer. Lutathera was subsequently approved by the US FDA in January 2018. Lutathera reduced the risk of disease progression or death in NET patients by 79% in pivotal studies.

In October 2017, soon after the EU approval, Novartis announced an offer to acquire the developer of Lutathera, Advanced Accelerator Applications (AAA), for US$3.9bn.

In a particularly relevant example of pharma interest, in February 2014 Bayer acquired Algeta for 16.2bn Norwegian kroner (~US$2.6bn). Algeta had developed Xofigo, a therapeutic radiopharmaceutical for patients whose prostate cancer had metastasised to their bones, which had been approved in the US and Europe in 2013. Bayer had previously entered a licensing agreement with Algeta in relation to Xofigo in 2009.

In an unrelated development, in 2017 the FDA approved Xofigo (Bayer), a bone-targeted alpha particle called radium 223, for patients whose prostate cancer has metastasised to their bones.

The global radiopharmaceutical industry is expected to grow to US$26bn by 2030 (from US$4.5bn in 2016)[1], which has stimulated increased interest from big pharma in the field. Telix is well placed to play an important part in the anticipated growth of the radiopharmaceutical industry.

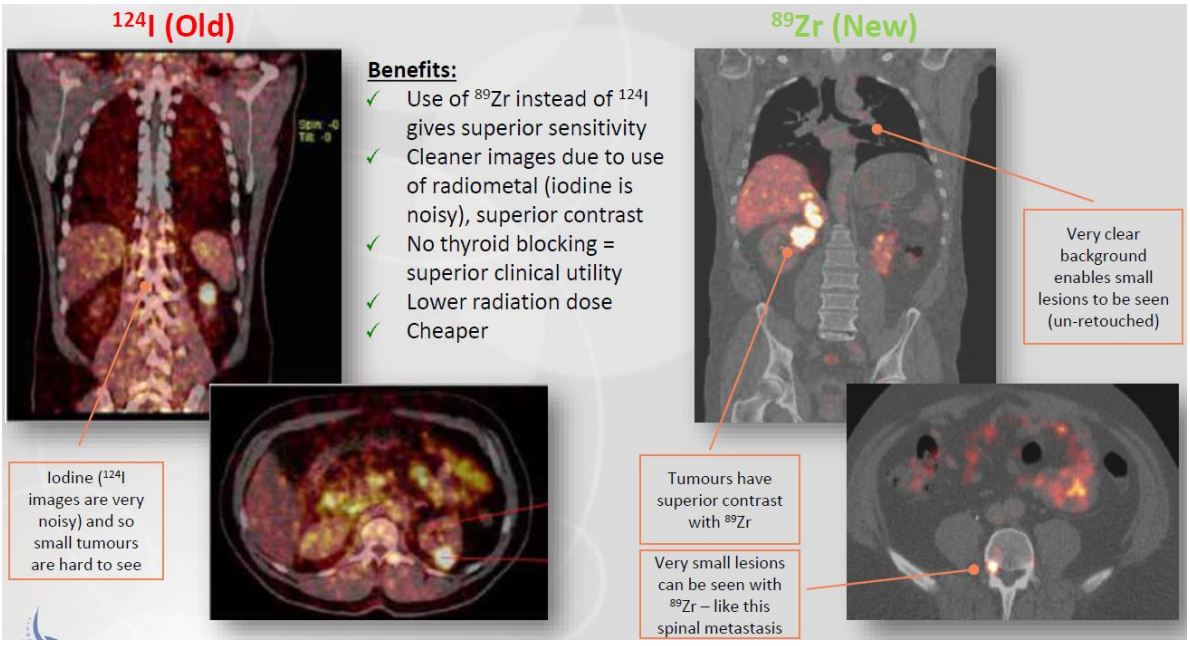
TLX250-CDx: Identifying dangerous kidney cancers

Telix is developing TLX250-CDx as an imaging agent to detect ccRCC, which is the most common and aggressive form of kidney cancer; ccRCC comprises around 70-75% of all kidney cancers. TLX250-CDx uses a radiolabelled antibody that binds to carbonic anhydrase 9 (CA-IX), which is highly expressed on the surface of over 90% of ccRCC tumours, but is not detectable in normal kidney tissues. CA-IX is also highly expressed in a range of other cancers including lung, cervical, ovarian, oesophageal and breast carcinomas[2].

TLX250-CDx is based on the mAb girentuximab (cG250) that Telix in-licensed from Wilex. Wilex developed an ^{124}I-labelled version of girentuximab for imaging with PET, that it named Redectane. In the studies conducted by Wilex, PET/CT scans were done two to six days (average five days) after Redectane infusion.

Telix has improved on the Wilex imaging product by replacing the ^{124}I radiolabel with ^{89}Zr. ^{89}Zr is a radio metal that becomes charge-trapped in the cytoplasm after the antibody bound to the CA-IX antigen on the surface is internalised and broken down within the cell, in contrast to ^{124}I which is quickly released from the cell. The fact that ^{89}Zr stays trapped within the cells results in an improved signal to noise ratio and clearer images, as can be seen in Exhibit 3. Exhibit 3 contrasts images obtained with the old ^{124}I radiolabel on the left hand side with the much sharper images obtained with ^{89}Zr-radiolabelled TLX250-CDx on the right.

Exhibit 3: TLX250-CDx produces much sharper images of ccRCC than the old Wilex product



Source: Telix Pharmaceuticals

1 MEDraysintell Nuclear Medicine World Market Report & Directory (2017 edition).

2 Pastorekova, S. et al. (2004) Cancer Therapy 2, 245–262

A test to identify whether a kidney lump is a dangerous cancer

ccRCC is the most dangerous kidney cancer and is the most likely to progress and metastasise (spread); it is four times as likely to develop distant metastases as the other less common, non-clear cell subtypes[3]. This means the key thing to know about a suspicious renal mass is whether or not it is ccRCC. This is becoming more important given that renal masses are increasingly being detected as incidental findings to abdominal imaging done for other reasons.

Unfortunately, in many cases current imaging techniques are unable to distinguish between ccRCC and benign tumours or less aggressive forms of kidney cancer. Surgical excision is the standard treatment of suspicious renal masses in patients who are otherwise healthy. However, a meta-analysis of 26 studies found that 15% of surgically resected renal masses were in fact benign[4] (non-cancerous), so many patients are having unnecessary surgery.

At a meeting in 2012, the FDA's Oncologic Drugs Advisory Committee (ODAC) concluded a test that could distinguish between ccRCC and other kidney masses would be useful when deciding how to manage renal masses. The ODAC concluded the test would be useful in the 20–30% of patients where the renal mass was considered indeterminate following examination by other imaging techniques such as ultrasound or CT. It was considered likely to be particularly useful for small lesions (1–2 cm) and for larger lesions in patients with poor overall health where the risks of surgery are greater.

Redectane shown to be significantly better than CT in Phase III, but confirmation needed

Wilex conducted a US-based Phase III study of Redectane in 196 patients with renal masses that were scheduled for surgical resection. In 2010 the study reported sensitivity and specificity for ccRCC of 86% and 87% respectively[5]. While the sensitivity and specificity for Redectane were significantly higher than for the contrast-enhanced CT scans (CECT), the study missed one of its four primary endpoints because the specificity was not significantly higher than the pre-specified arbitrary target of 75% (p=0.057). This miss was due to the smaller than intended number of non-ccRCC patients in the study (53 vs the expected 63 non-ccRCC patients). Despite the 16/0 positive ODAC vote regarding the potential usefulness of an imaging test with the characteristics of Redectane, the FDA declined to approve Redectane and requested that Wilex undertake a confirmatory Phase III study; due to funding limitations Wilex did not conduct the requested study.

ccRCC imaging Phase III to follow bridging study

Having in-licensed the programme from Wilex, Telix has commenced the first stage of a confirmatory Phase III trial using its improved version of Redectane that it has termed TLX250-CDx. It has already recruited four of the 10 patients required for a dosimetry/bridging study to confirm the utility of replacing the old ^{124}I isotope with the new ^{89}Zr isotope, which is expected to complete in Q318. At the completion of the bridging study the ZIRCON Phase III trial will be expanded to recruit up to 200 patients at ~15 European sites (expected in Q418). Up to three Australian sites and up to eight US sites are also expected to join the study once it is up and running and to recruit up to 100 additional patients into the study. Management believes the Phase III study will complete by Q319.

3 Kim et al., Urol 2011; 78:1101-1106

4 Corcoran et al (2013) Urology. 2013 Apr;81(4):707-13

5 Divgi et al 2012 J Clin Oncol 31:187-194

Kidney cancer incidence

According to the National Cancer Institute, kidney cancer is the eighth most common cancer, and is expected to account for 65,340 new cases and 14,970 deaths in the US in 2018. Globocan predicts that in 2020 there were will be 413,000 cases and 176,000 deaths from kidney cancer worldwide, while in the EU in that year there are predicted to be 94,900 new cases and 39,800 deaths.

At the time of diagnosis, the disease is localised to the kidney in 65% of cases, while it has spread to regional lymph nodes in 16% of cases and has metastasised elsewhere in the body in a further 16% of cases (staging is unknown in 3% of cases). While the overall five-year survival rate is 75%, the prognosis ranges from a five-year survival of 93% for patients diagnosed with localised tumours to a low 12% for patients who have metastatic disease at diagnosis.

There is a significant potential market for TLX250-CDx in renal cancer imaging

Taking the midpoint of the assessment by the ODAC that an imaging test with properties similar to TLX250-CDx would be useful in 20–30% of patients with a renal mass, we assume that 25% of RCC patients would be candidates for an imaging indication similar to that sought by Wilex to assist in the characterisation of ccRCC as part of the diagnostic work-up of an indeterminate renal mass.

In addition to use in the initial diagnostic workup, the test could also be used to:

- detect metastatic disease;
- screen patients for suitability for MTR therapy with TLX250; and
- potentially monitor response to therapy with targeted agents such as sunitinib (Sutent).

We suspect these additional indications could potentially be several times larger than that for initial diagnostic work-up of an indeterminate renal mass, but we conservatively model the potential market for these indications as the same size as that for the initial work-up (ie 25% of new cases), taking the total addressable market to 50% of new RCC cases each year.

Alternative diagnostic methods for renal masses

High resolution CT is the first choice for imaging renal masses, but while a CT scan tells you about the structure of the mass it does not tell you about the biology. Currently, a renal mass that is enhanced on CT is considered malignant until proven otherwise as there is no alternative imaging agent that can identify ccRCC tumours.

A tissue biopsy can be used to identify cancerous renal masses, including ccRCC, but less than 10% of suspicious renal masses are biopsied in clinical practice due to the risks associated with collecting the biopsy tissue sample and because the rate of non-diagnostic biopsies is 10% to 20%[6].

FDG-PET has limited utility for diagnosis of primary RCC as the renal uptake is likely to be masked by the excretion of the agent in the urine[7]; it is more useful for detecting metastases distant from the kidney.

An alternative strategy when investigating indeterminate real masses could be to actively highlight benign masses. A number of small studies have been conducted on the use of a mitochondrial imaging agent ^{99m}Tc-sestambi single photon emission CT (SPECT) to identify mitochondrial-rich benign and indolent (slow growing) renal masses such as oncocytomas and hybrid

6 Divgi et al 2012 J Clin Oncol 31:187-194

7 Sankineni et al (2016) Urologic Oncology: Seminars and Original Investigations 34 (2016) 147–155

oncocytoma/chromophobe tumours. In a recent study[8], ^{99m}Tc-sestamibi successfully identified all 7/7 ccRCC tumours as not being benign/indolent, and identified 16/24 (67%) of non-ccRCC tumours as being benign/indolent types.

As ^{99m}Tc sestamibi is already used for clinical investigations of myocardial perfusion and for the detection of parathyroid adenomas, it could potentially also be used to aid in the identification of benign/indolent renal masses in the clinic if sufficient evidence becomes available to justify its use. However, the lower image resolution of SPECT imaging means that it is not well suited to imaging small lesions. In addition, ^{99m}Tc sestamibi would not be suitable for any of the other potential applications of TLX250-CDx, such as detection of ccRCC metastases, assessing response to therapy or screening for suitability for TLX250 MTR therapy.

TLX250 ccRCC therapeutic

Telix is also developing TLX250, a MTR therapeutic targeting ccRCC. TLX250 is based on a modified and improved version of the mAb girentuximab (cG250) labelled with the isotope ^{177}Lu. ^{177}Lu is an ideal isotope for therapeutic MTR applications because it emits beta particles that travel only a short distance in tissue and are absorbed within the tumour, killing cancer cells. It has a comparatively short half-life of 6.64 days.

Wilex has completed two clinical studies of ^{177}Lu-cG250 in patients with metastatic ccRCC. The two studies provided encouraging evidence of efficacy, with 78% and 68% of patients achieving responses of stable disease or better in the three months after the first course of treatment in the Phase I and Phase II studies, respectively. One of the 14 patients in the Phase II study achieved a partial response. While the treatment was generally well tolerated, a high proportion of subjects experienced myelosuppression (low levels of white blood cell production in the bone marrow). We expect the company to seek to optimise the dosing regimen (both amount and interval) in future studies to in order to reduce the incidence of this side effect. The company's experience with MTR therapies in prostate cancer will help inform the programme to optimise the dosing regimen.

Better treatments are needed for metastatic ccRCC

While many patients who are diagnosed with early-stage RCC can be cured by surgical treatment, better treatments are needed for metastatic disease, where the five-year survival rate is only 12%.

Checkpoint inhibitors and targeted therapies (antiangiogenic therapies and mTOR inhibitors) are the mainstays of systemic treatment for unresectable and metastatic ccRCC, rather than cytotoxic chemotherapy. According to clinical guidelines, the preferred first-line therapies are the targeted therapies pazopanib and sunitinib; ipilimumab + nivolumab combination (FDA approved April 2018) is a preferred first-line therapy for intermediate and low risk patients, but not for high-risk patients[9].

Preferred second-line therapies are cabozantinib (TKI including VEGFR) and the anti-PD1 immune checkpoint inhibitor (ICI) nivolumab, which was approved by the FDA for patients with advanced RCC in November 2015.

Potential for TLX250/ICI combo to improve response rates

Therapies such as ICI that enhance immune responses have had remarkable success in treating a range of cancers, however, typically less than a third of patients respond when these drugs are

8 Tzortzakakis et al. EJNMMI Research (2017) 7:29

9 National Comprehensive Cancer Network (NCCN) Kidney Cancer Guidelines version 4.2018

used as single agents (monotherapy). For example, the response to second-line treatment of mRCC with nivolumab was 22%[10].

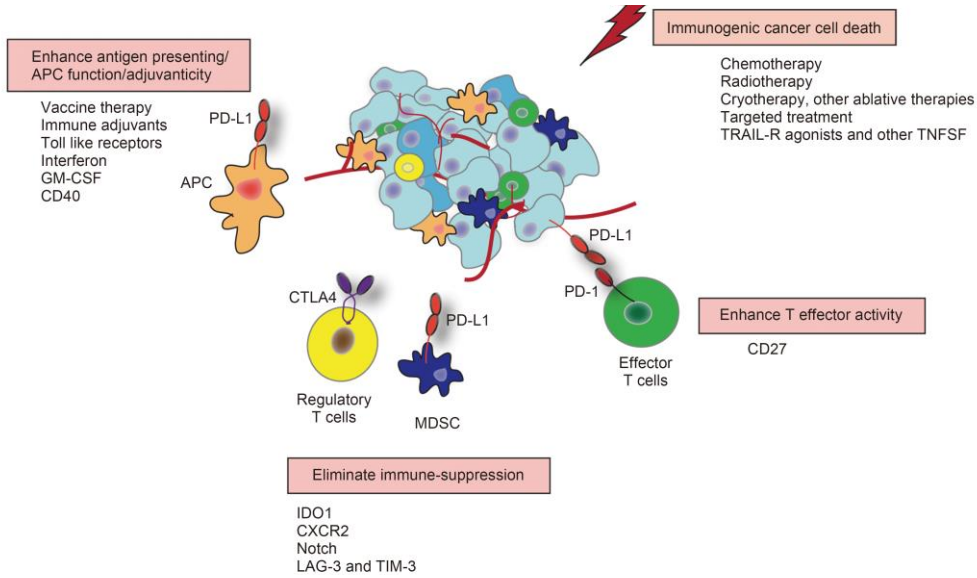
Combining ICI with chemotherapy has been an effective way to improve response rates compared to ICI monotherapy in a number of cancer types. For example, in newly diagnosed metastatic lung cancer the response rate to the Keytruda/chemo combo in the KEYNOTE-189 study was 49.4%[11], which is substantially higher than the 27.3% ORR to Keytruda monotherapy reported in the separate KEYNOTE-042 study. The synergistic benefit of ICI/chemo combos is believed to be due to the cellular debris from tumour cells killed by the chemotherapy triggering an immune response (sometimes referred to as immunogenic cancer cell death or turning immunologically cold tumours hot), with the ICI then able to strengthen this immune response.

With chemotherapy not recommended in ccRCC, there is potential for MTR to play a similar role in killing tumour cells and releasing tumour antigens to stimulate an immune response. Combining MTR with ICI would be expected to improve ORR.

The ability of radiation therapy to have immune stimulatory effects is evidenced by the well-established phenomenon of so-called abscopal responses to radiation, where tumours away from the site of radiation also respond to treatment due to an immune response triggered by the therapy[12].

Exhibit 4 shows how both chemotherapy and radiotherapy can cause immunogenic cancer cell death and thus play a role in initiating an anti-tumour immune response.

Exhibit 4: Potential combination strategies to improve response rates to ICI therapy



Source: Harris et al. Cancer Biol Med 2016 13(2). doi: 10.20892/j.issn.2095-3941.2016.0015

Furthermore, a randomised trial presented at ASCO in June provided direct evidence that radiation therapy can enhance responses to ICI therapy. In the PEMBRO-RT study in 64 patients with lung cancer, combining external beam radiation therapy with the ICI pembrolizumab improved ORR to 41% vs 19% for pembrolizumab alone. Median PFS was 6.4 months for the combo vs 1.8 months for pembrolizumab alone (HR 0.55, p=0.04)[13].

10 Opdivo prescribing information

11 Gandhi et al. N Engl J Med 2018;378:2078-92.

12 Shabason et al 2017, Semin Radiat Oncol 27:289-298

13 Theelen et al 2018, ASCO abstract 9023

We see good potential for TLX250 to be combined successfully with ICI therapy. However, it could potentially face competition from a form of external beam radiation therapy called stereotactic body radiation therapy (SBRT; also known as SABR) in patients who have only a small number of metastatic sites[14].

Phase II trials for TLX250 planned for 2019

Telix is formulating plans for three Phase II studies of TLX250 in combination with ICIs, one of which is likely to be a pharma-sponsored study. The three studies are expected to involve ~60 subjects in total. It plans to submit two INDs in relation to these studies in US/Australia in Q418. The manufacture of clinical grade material for these studies is expected to be completed by the end of August.

By the end of 2019 the company expects these studies to have produced sufficient information to identify an appropriate strategy for the Phase III development of TLX250. A key goal of the planned Phase II studies is to demonstrate that there are synergistic benefits from combining TLX250 with ICI therapy.

TLX591-CDx for imaging prostate cancer

Telix is also developing TLX591-CDx (^{68}Ga-HBED-PSMA-11), a small-molecule MTR diagnostic for imaging prostate cancer. TLX591-CDx targets the prostate specific membrane antigen (PSMA), which is expressed in very high levels in the prostate but in low levels on most other normal cells. PSMA is significantly over-expressed in prostate cancer cells and some other solid tumours[15]. Prostate cancer overexpression has been shown to be 100-fold to 1,000-fold that of normal tissue expression[16].

TLX591-CDx is based on PSMA-11, a peptide ligand that binds to the PSMA protein. PSMA-11 labelled with the ^{68}Ga radio isotope has been widely used in academic medicine in Europe and Australia to image prostate cancer, and has been shown to be safe to use and to produce high quality images (Exhibits 5 and 6).

While the PSMA-11 targeting agent (ligand) is in the public domain, the chemistry for linking the ^{68}Ga radiolabel to the ligand and preparing the dose of the imaging agent with the TLX591-CDx kit utilises is proprietary chemistry developed by ANMI SA of Belgium.

ANMI has developed a so-called ‘shake and shoot’ kit. The kit contains all of the components needed to attach the ^{68}Ga radiolabel to the PSMA targeting agent. The radioactive ^{68}Ga is produced in the hospital pharmacy by elution from a column of ^{68}Ge, which is gradually converted to ^{68}Ga by radioactive decay. The kit takes only a few minutes to prepare an injection-ready dose, with all of the steps done at room temperature. The prepared radiolabelled product can then be injected into patient, who is then imaged in a PET scanner an hour or so later.

Telix has formed a JV with ANMI for the development and subsequent commercialisation of TLX591-CDx in the US. The US JV, known as Kyzeo Imaging, has completed validation at a US clinical site and a DMF has been reviewed and accepted by the US FDA. A DMF is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs. A third party can incorporate the information in a DMF into an IND or NDA application by way of a letter from the manufacturer (Telix) to the applicant, which authorises reference to the DMF.

14 Siva et al 2017. Nature Reviews Urology; 14. 549-563

15 Sterzing et al; Eur J Nucl Med Mol Imaging (2016) 43:34–41

16 Evans et al. Practical Radiation Oncology, 2018 8, 28-39

Now that the DMF has been reviewed, TLX591-CDx can be sold as an investigational product kit for use under an IND that references the DMF. The Memorial Sloan Kettering Cancer Center (MSKCC) recently launched an expanded-access study (NCT03204123), which allows the kit to be used to image prostate cancer patients at its clinics. Telix has granted Endocyte access to the DMF and is supplying TLX591-CDx kits to Endocyte for screening patients in its VISION Phase III prostate cancer trial.

Telix is in active discussions with distributors and plans to commercially launch TLX591-CDx in Q318. It has already encountered significant clinical interest or demand from over 50 hospital networks in the US. Telix believes its strategy of commercialising TLX591-CDx as an investigational test will give it the first ^{68}Ga-based PSMA product for PET imaging widely available in the US. Imaging sites could be authorised to image patients using TLX591-CDx via a simple IND application supported by the DMF. As far as we could determine, no other company has submitted a DMF for a PSMA PET imaging product to the FDA[17].

Exhibit 5: Examples of PSMA-11 imaging of low, medium and high prostate cancer tumour burden

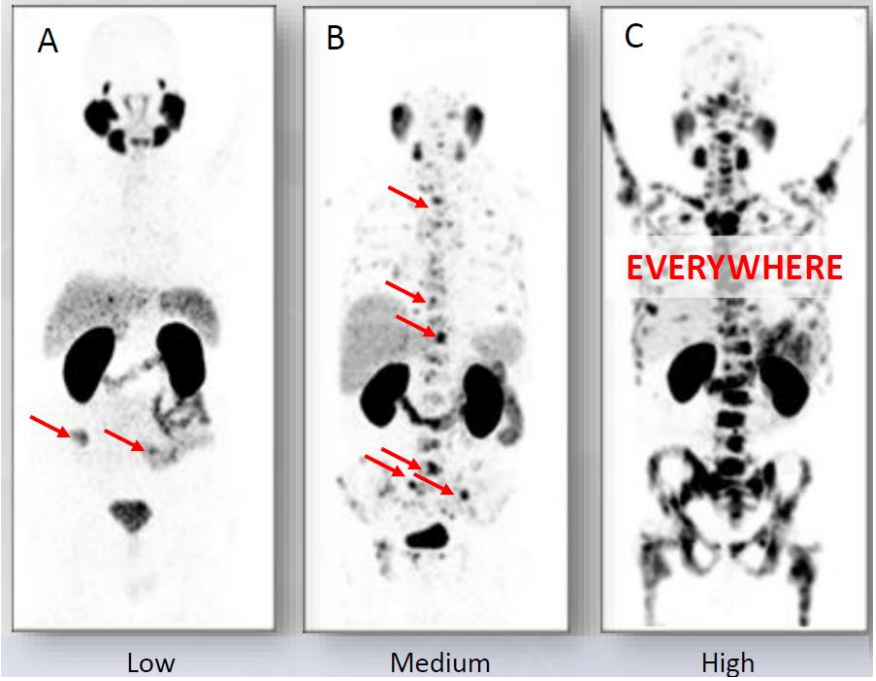
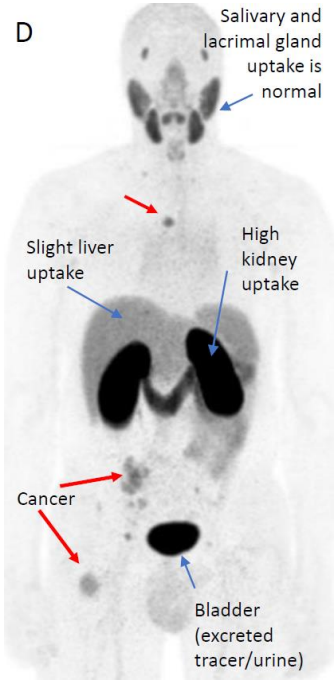


Exhibit 6: Typical biodistribution of PSMA-11 tracer



Source: Telix Pharmaceuticals. Note: Red arrows mark some of the more prominent prostate cancer tumours.

Potential quick route to FDA approval

While TLX591-CDx is initially being commercialised as an investigational test in the US, Telix intends to seek full FDA approval, which would bring higher reimbursement and allow active marketing of the test.

The FDA has already shown it is willing to approve a prostate cancer PET imaging agent on the basis of blinded, independent reads of existing patient scans. In May 2016 it approved Axumin (^{18}F-fluciclovine, Blue Earth Diagnostics) based on two studies that utilised re-reads by three blinded independent readers of scans that had previously been read by on-site readers; in each study the scans were from men with suspected recurrence of prostate cancer based on rising PSA levels. In the first study in 105 men, the Axumin PET scans were compared to histopathology obtained by

17 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM370722.xls

biopsy of suspicious lesions. In the second study in 96 men, Axumin PET scans were compared to PET scans with ^{11}C-choline.

Telix already has access to data from historical TLX591-CDx PET scans in Europe, and will receive additional scan data from the MSKCC and Endocyte trials. It plans to hold a pre-NDA meeting with the FDA in Q418 where it will propose a Phase III programme for TLX591-CDx that is based on blinded re-reads of existing data. If this strategy is acceptable to the FDA, then management anticipates an NDA submission in 2019. Given that the FDA has already reviewed the manufacturing and QC data in the DMF, there is the potential that TLX591-CDx could be approved by the FDA by the end of 2019 (we model a more conservative timeline with a potential approval in 2020). The estimated cost of a Phase III study and NDA filing based on re-reads is US$2m.

Prostate cancer incidence

According to the National Cancer Institute, prostate cancer is the second most common cancer in men; it is expected to account for 165,000 new cases and 29,400 deaths in the US in 2018, while 2.9m men in the US are estimated to be living with a diagnosis of prostate cancer. Globocan predicts that in 2020 there will be 1,393,000 cases and 386,000 deaths from prostate cancer worldwide, while in the EU in that year there will be 398,000 new cases and 84,000 deaths. At diagnosis, the disease is localised to the prostate in 78% of cases, while it has spread to regional lymph nodes in 12% of cases, and has metastasised elsewhere in the body in a further 5% of cases (staging is unknown in 4% of cases). While the overall five-year survival rate is very high at 98.2%, the prognosis ranges from a five-year relative survival of 100% for patients diagnosed with localised tumours to only 30% for patients who have metastatic disease at diagnosis.

Clinical utility and market opportunity for PSMA-based imaging in prostate cancer

The PSA blood test is the main tool used for monitoring prostate cancer patients for disease recurrence. An estimated 15-30% of patients experience rising PSA levels (biochemical recurrence) after prostatectomy surgery or radiation therapy. In our view, the main application for TLX591-CDx imaging is likely to be for detecting prostate cancer metastases in men with biochemical recurrence for whom the site of metastasis or recurrence can't be identified by standard imaging methods such as CT, MRI or bone scintigraphy.

A second potential indication for TLX591-CDx would be to screen newly diagnosed patients assessed as having high-risk disease, based on biopsy results, for metastases to pelvic lymph nodes as well as distant sites. For both of these indications a key aim of the imaging would be to identify the site of metastasis or recurrence so it can be treated by surgery or radiation therapy.

In assessing the addressable market for TLX591-CDx, we bear in mind that while 15-30% of prostate cancer patients experience biochemical recurrence, only a proportion of these cases will be unable to find the metastases by standard methods. On the other hand, some men may have multiple recurrences or may have multiple PSMA scans if the initial scan does not identify any metastases following biochemical recurrence. Weighing up all of these factors, we believe that 50% of the number of men diagnosed each year is a reasonable estimate of the potential demand for PET scans in men with biochemical prostate cancer recurrence.

In regard to the second potential indication in newly diagnosed prostate cancer, we note that 20-30% of men diagnosed with localised prostate cancer present with high-risk tumour characteristics.[18] Combining the midpoint of 25% for the incidence of high-risk prostate cancer with our estimate of 50% for biochemical relapse requiring PET imaging, our estimate of the total

18 Punnen et al. Current Opinion in Urology: 2013 23(4), 331–336

addressable market is 75% of the number of men diagnosed each year, which is equal to 91,000 scans per year in the US.

Comparing prostate cancer PET imaging technologies

A number of targeted agents for PET imaging of prostate cancer have been investigated, in addition to ^{68}Ga PSMA-targeting products. Most interest has focused on ^{68}Ga or ^{18}F-babelled PSMA, ^{11}C or ^{18}F labelled choline and ^{18}F fluciclovine, which is marketed as Axumin.

Exhibit 7 shows that the sensitivity and specificity PSMA and choline PET imaging products for detecting recurrent prostate cancer are equivalent at 85-89%. While the sensitivity of fluciclovine/Axumin is high the specificity is low, which means there will be a high number of false positive reports. For comparison, Exhibit 7 also includes ^{18}F-FDG, which is widely used to detect metabolically active cancers such as lung, colorectal and breast cancers, but is not a sensitive test for prostate cancer, which is less metabolically active than many other cancers.

Exhibit 7: Sensitivity and specificity of radiotracers for detecting prostate cancer recurrence

	PSMA	Choline	Fluciclovine	Axumin (FDA label)*	^{18}F -FDG	ProstaScint
Sensitivity	86%	85-89%	87%	95%	26-57%	49%
Specificity	86%	88-89%	66%	31%		71%

Source: Edison Investment Research; Evans et al. Practical Radiation Oncology (2018) 8, 28-39; Taylor et al. Trends in Urology & Men's Health 2014 5(3), 34-37; ProstaScint product label. Note: Sensitivity and specificity for Axumin calculated by Edison from data in the Axumin Prescribing Information label.

A key advantage of PSMA imaging agents is that they are more sensitive than other agents for detecting metastases in biochemically recurrent prostate cancer where the PSA levels are low (ie when the tumours are small). In the studies included in a review of prostate cancer PET radiotracers[19], the sensitivity of PSMA PET for detecting recurrent prostate cancer metastases in men with low PSA levels (<2.0 ng/ml) was 67%, vs 41% for fluciclovine and 34% for choline. Given it is these small metastases that are the most difficult to detect with standard imaging methods, we expect the increased sensitivity in this patient group will see PSMA PET become the preferred imaging technology for recurrent prostate cancer.

We expect a key driver of uptake of the TLX591-CDx shake and shoot kit will be that it is as well suited to smaller clinics as it is to large hospital sites, because it does not require access to a cyclotron to generate the radioisotope or a centralised manufacturing facility to generate the imaging agent.

Prostate imaging competitors in the US market

While the FDA has not approved any PET imaging agents that target PSMA, it has approved prostate cancer imaging agents based on choline and fluciclovine. The availability of prostate cancer-specific PET imaging is rapidly expanding in the US; as of 2017 it was available at 34 sites – eight using ^{68}Ga or ^{18}F PSMA, eight using ^{11}C or ^{18}F choline and 18 using Axumin[20].

Axumin (Blue Earth Diagnostics) was approved by the FDA in May 2016 and by the European Commission in May 2017. It is indicated for PET imaging in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment, and has subsequently been included in the National Comprehensive Cancer Network clinical guidelines for this indication. Axumin contains the ^{18}F-labeleld synthetic amino acid analogue fluciclovine. ^{18}F fluciclovine is taken up by amino acid transporters such as ASCT2 and LAT-1 and accumulates to a greater extent in prostate cancer cells compared with the surrounding normal tissues. Blue Earth reported

19 Evans et al. Practical Radiation Oncology, 2018 8, 28-39

20 Evans et al. Practical Radiation Oncology (2018) 8, 28-39

global sales for the year to September 2017 of £15.8m (~US$21m), mostly from the US market (vs £0.5m in the preceding year). Sales in the six months ending March 2018 were £23.5m (US$30m). Blue Earth sold 3,700 Axumin units in the US in Q417, 5,000 units in Q118 and 6,000 units in Q218.

The FDA approved manufacture and use of a second agent, ^{11}C choline, for PET imaging in recurrent prostate cancer at the Mayo Clinic in 2012. Choline has subsequently been approved at three other hospitals as well as for manufacture and supply by the radio-pharmaceutical manufacturer Zevacor Molecular. Choline is an essential component of cell membranes and accumulates in tissues with high cellular proliferation.

Other companies are developing PSMA PET agents for the US market

Despite the fact that the FDA has not approved any PET imaging agents that target PSMA, we noted above that as of 2017 at least eight institutions were providing a PSMA-PET imaging service as an investigational agent. A number of other companies are also developing PSMA-based PET imaging products, so Telix may face direct competition from an approved PSMA imaging test in the US, in the future. Four potential competitors are described briefly below.

Progenics (NASDAQ: PGNQ) has completed enrolment in a Phase II/III study of a PSMA-based PET imaging agent ^{18}F -DCFPyl, which was developed at Johns Hopkins. The study enrolled 383 patients with localised high-risk prostate cancer or recurrent or metastatic disease and is expected to report top-line data in Q418. A second Phase III in patients with biochemical recurrence is expected to commence in Q418.

The UK-headquartered, privately owned company Theragnostics has developed a room-temperature 'shake and shoot' kit for ^{68}Ga -THP-PSMA (also known as THG-001), which sounds similar to the ANMI technology used with TLX591-CDx. Theragnostics recruited the first patient in a Phase II study in high-risk or recurrent prostate cancer in June 2018, but does not appear to be supplying the product on a commercial basis in the US.

Novartis also recently entered the field when its recently acquired subsidiary Advanced Accelerator Applications signed a licence agreement with US-based private company Cancer Targeted Technology to develop and market CTT1057. CTT1057 is an ^{18}F -based PSMA tracer, which recently completed a Phase I clinical trial.

In May 2018 Blue Earth diagnostics in-licensed global rights to a family of ^{18}F-PSMA MTR imaging agent from Scintomics. The acquisition of this preclinical PSMA imaging programme suggests to us that Blue Earth expects PSMA diagnostics to play a key role in prostate cancer imaging.

For completeness, we mention much older PSMA imaging technology ProstaScint, an ^{111}In-labelled mAb that targets an intracellular PSMA epitope, which the FDA approved in 1996. ProstaScint (Aytu Bioscience; NASDAQ: AYTU) uses an older imaging technology, SPECT scan, which is much less sensitive than the PET imaging technologies described above (Exhibit 7). ProstaScint is approved as a diagnostic imaging agent for detecting lymph node metastases before surgery in patients with high-risk, biopsy-proven prostate cancer, and for post-surgery patients with rising PSA and negative or equivocal standard metastasis evaluation. However, sales have been modest and Aytu intends to withdraw ProstaScint from the market in the US at the end of 2018.

Pricing for prostate cancer imaging agents

US Medicare reimburses Axumin at US$3,900 per dose, while ^{11}C choline is reimbursed at US$5,700 per dose[21]. Medicare typically reimburses drugs on a pass-through basis for three years, after which the cost of the drug is packaged into the overall procedure cost. We model average revenue to the JV of US$3,500 per procedure.

21 http://www.triadisotopes.com/sites/default/files/blog/downloads/triad_icl_dec_2017_final.pdf

TLX591 prostate cancer therapeutic

Telix is developing TLX591, a ^{177}Lu-labelled MTR therapeutic for treating prostate cancer. TLX591 is based on an enhanced version of the huJ591 mAb.

Telix has a research collaboration and option agreement with Atlab Pharma, a privately owned French biotech, which holds the right to the huJ591 antibody for use with ^{177}Lu and certain other combination therapy rights. Atlab in-licensed the rights from Cornell. Telix is exercising its option to acquire Atlab for ~US$10m.

Atlab conducted a number of clinical trials of a single cycle of treatment with ^{177}Lu-J591 (which Atlab called ATL101), in conjunction with Weill Cornell. When ^{177}Lu-J591 was administered as a single infusion, the MTD was 70 mCi/m2 and 11-12% of subjects treated at 65 or 70 mCi/m2 achieved at least a 50% reduction in PSA count.

The tolerability was improved in a subsequent study by splitting the total dose into two fractions administered two weeks apart. The total dose tolerated as two fractions was higher at 80-90 mCi/m2 (2x40 mCi or 2x45 mCi with the option of GCSF white blood cell growth factor). The higher total fractionated dose was also more efficacious; 21% of subjects treated at the RP2Ds experienced a 50% reduction in PSA, including 29% of subjects treated at the highest dose of 2x45 mCi[22].

In a separate study when a single cycle of fractionated ^{177}Lu-J591 was administered in combination with a multiple cycles of docetaxel chemotherapy, 11/15 (73%) of subjects achieved at least a 50% reduction in PSA levels[23].

In each study of ^{177}Lu-J591 the dose-limiting toxicity was reversible myelosuppression, a condition where bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets.

In the Phase I study of dose fractionated ^{177}Lu-J591, 36/49 (74%) subjects treated in all six dose cohorts had grade 3/4 haematological toxicity, while 19/33 (58%) of subjects treated at the RP2D had the more severe grade 4 haematological toxicity. In the docetaxel combo study, 20% experienced grade 4 neutropenia without fever, while 13% experienced grade 4 thrombocytopenia.

Overall, the studies showed that fractionated ^{177}Lu-J591 is tolerated with subsequent PSA declines and reversible myelosuppression. The falls in white blood cell counts were severe but did not result in fever (so-called febrile neutropenia, which can be life-threatening). While the haematological toxicity/myelosuppression increases the risk of bleeding events or infection, it does not otherwise impair patient quality of life, unlike, for example, nausea, diarrhoea or neuropathy often associated with chemotherapy. However, neutropenia can result in a delay in subsequent chemotherapy treatment if the patient progresses despite MTR therapy.

TLX591 has been reengineered to improve tolerability and efficacy

While TLX591 is based on ATL-101/^{177}Lu-J591, Telix has made a number of modifications to optimise its performance. It has been re-humanised, stability/affinity optimised, and re-engineered to have better properties for radioactive drug use.

In general, at high doses radio-labelled mAbs have higher haematologic toxicity than small molecules because of their long circulation time (around one week serum half-life) compared to around a 48 hour clearance from radio-labelled peptides. To address this, Telix has modified the

22 Tagawa et al; ASCO 4 June 2016. J Clin Oncol 34, 2016 (suppl 15; abstr 5022)

23 Batra et al; ASCO Genitourinary Cancers Symposium 2015. J Clin Oncol 33, 2015 (suppl 7; abstr 199)

constant region of the TLX591 mAb to stop it binding to the Fc receptor on white blood cells. As a result, TLX591 is cleared from the bloodstream much more rapidly, which is expected to result in less haematologic toxicity.

While the company anticipates that TLX591 will have better efficacy and fewer toxic side effects than ^{177}Lu-J591, this will need to be tested in clinical studies.

TLX591 development plan

Drug material for toxicology and human biodistribution studies is expected to be ready by the end of 2018. The company is planning to conduct initial biodistribution/pharmacology studies for TLX591 in Australia. It is on track to initiate an Australia/US multi-centre Phase II study in mid-2019.

Endocyte launches a Phase III trial of ^{177}Lu-PSMA-617 after 62% response rate in Phase II

Although TLX591 (^{177}Lu-J591) has shown encouraging efficacy in clinical studies, Telix may face competition in this space from Endocyte's small molecule therapeutic ^{177}Lu-PSMA-617, which also binds to the PSMA receptor and reported high response rates and low toxicity in a Phase II study in metastatic castration resistant PC (mCRPC). Preliminary data reported by Endocyte at ASCO in June from the 50-patient Phase II study showed that 62% of subjects experienced a PSA decline of at least 50%. The treatment was well tolerated, with the most common side effect being grade 1–2 dry mouth reported by 68% of subjects (66% grade 1, 2% grade 2). The occurrence of grade 3–4 hematologic toxicity was low; there were no cases of grade 4 neutropenia and only 6% of subjects experienced grade 3 neutropenia. Patients were dosed every six weeks for up to four cycles.

In June 2018 Endocyte enrolled the first patient in a 750-patient global Phase III study of ^{177}Lu-PSMA-617 in PSMA-positive mCRPC. The dose in the Phase III study is 7.4GBq every six weeks for up to six cycles. Endocyte is using Telix's TLX591-CDx kit to screen patients for enrolment into the trial.

Bone-targeted prostate cancer radiotherapeutics show the way

In 2013 the FDA approved Xofigo (Bayer), a bone-targeted alpha particle called radium 223, which leads to longer overall survival in men who have with symptomatic mCRPC with bone metastases but no known metastases in visceral organs. In a Phase III study, Xofigo improved survival by 3.6 months (14.9 months versus 11.3 months; HR, 0.70).[24]

At its launch in 2013, Xofigo was priced in the US at US$69,000 for a course of six injections four weeks apart. We estimate that, since then, the manufacturer's list price has increased to currently be ~US$91,000 for a course of treatment with Xofigo. We base this estimate on the wholesale acquisition cost or WAC of US$131.85 per mCi, the recommended dose of 1.35 mCi/kg and average weight of a US male aged 60-80 of ~85kg. Worldwide sales of Xofigo in 2017 totalled €408m, including €242m in the US (US$492m and US$292m, respectively). Bayer expects peak sales of Xofigo to be in excess of €1bn (US$1.2bn), although the increased death rated reported in patients receiving Xofigo plus Zytiga in a recent Phase III study in chemotherapy-naïve patients with no symptoms or only mild symptoms may limit future sales growth. In the US there are also older FDA-approved treatments utilising radioactive isotopes to reduce pain from prostate cancer that has spread to the bones, called samarium-153 (Quadramet) and strontium-89 (Metastron).

While these bone-targeted radioisotopes are useful because prostate cancer commonly spreads to bone, those drugs cannot treat tumours in other sites such as in the prostate, lymph nodes, or lung.

24 https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf

Given that TLX591 could be used to treat patients with soft tissue metastases as well as bony metastases, it would be applicable to a greater proportion of prostate cancer patients than Xofigo.

TLX101 therapeutic for brain cancer (glioblastoma)

In October 2017 Telix acquired the privately held German company Therapeia, which held and developed the background technology to TLX101.

TLX101 is a radiolabelled amino acid analogue (4-[^{131}I]iodo-L-phenylalanine, also known as ^{131}I-IPA), which is a small molecule that rapidly crosses the blood-brain barrier. TLX101 is taken up by the membrane-bound L-amino acid transporter 1 (LAT1), which is over-expressed in gliomas (brain cancers) including glioblastoma (GBM). This allows the tissue-specific accumulation of the ^{131}I therapeutic radionuclide inside the cancer cells. The ^{131}I radiolabel is used because it readily crosses the blood brain barrier, whereas a charged radiometal such as ^{177}Lu does not.

In addition, preclinical studies show that unlabelled IPA is a radio-sensitiser, ie, it increases the sensitivity of cells to radiation. In studies in an animal model where GBM tumours were growing in the brain of rats, combining TLX101 with external-beam radiation therapy (EBT) was much more effective than either therapy alone[25].

Telix also acquired TLX101-CDx which uses IPA labelled with the radionuclide ^{124}I for PET imaging, which Telix will use as a research tool to study the pharmacology of TLX101. PET imaging of patients with commercially available MTR diagnostics that cross the blood brain barrier and are taken up by LAT1, such as ^{18}F-FET or ^{18}F-flucyclovine (FACBC), could potentially be used to screen patients for enrolment in the upcoming clinical trials of TLX101

IPA labelled with a different radioisotope, ^{123}I, has previously been investigated for SPECT imaging of high grade gliomas. It showed uptake and prolonged retention and promising diagnostic performance. In an academic study in 100 patients with glioma the sensitivity to detect glioma was 88% with specificity for glioma of 95%. The sensitivity for high grade gliomas (mainly GBM) was 93%, therefore the vast majority of GBM patients should be eligible for therapy with TLX101.

A total of 11 patients have been treated with ^{131}I-IPA (TLX101) on a compassionate use basis in two institutions in Germany. Baum et al. (2011)[26] reported that among two patients with low-grade glioma treated with TLX101, one experienced a reduction in tumour volume over 10 months, with progression occurring 10 months after therapy. The second patient showed stable disease on MRI and PET during the three-month follow-up period. There was no clinically detected toxicity. Company data shows that, subsequent to the published study, the second patient was treated with ^{131}I-IPA + 68 Gy EBT, which resulted in a measurable (40%) reduction in tumour volume and clinical improvement including the cessation of epileptic fits. In addition, a patient with GBM who was treated with 6 GBq ^{131}I-IPA + 68 Gy EBT achieved histologically confirmed tumour eradication,[27] although the patient died eight months later from (unrelated) gastrointestinal bleeding.

TLX101 development plan

The company intends to conduct the IPAX-1 Phase I/II trial of TLX101 in at least 35 (potentially up to 55) relapsed GBM patients in connection with external-beam radiation therapy. The study will begin with a dose escalation component in ~20 patients. The efficacy assessment will be based on post-treatment imaging and is expected to read out by the end of 2019. If the trial is successful it

25 Samnick et al 2009. J Nucl Med. 2009 Dec;50(12):2025-32. doi: 10.2967/jnumed.109.066548

26 Baum et al 2011. Nucl Med Mol Imaging; DOI 10.1007/s13139-011-0116-6

27 https://www.therapeia.info/en/therapy/

would provide sufficient clinical data to decide whether to proceed to a Phase III trial. TLX101 has orphan drug designation in the US and Europe.

The twin aims of combining TLX101 MTR with EBT are to exploit the radio-sensitising properties of TLX101 and to maximise the dose of radiation delivered to the tumour without increasing the incidence of dose limiting toxicities. The dose of radiation delivered to the tumour can be maximised because the side effects of MTR and EBT affect different tissues. The side effects of EBT are due to the effect on other parts of the brain in the path of the X-ray beam, while the side effects of MTR are due to its accumulation in non-target tissues. Because there is very little overlap in the tissue distribution, combining the two modalities of radiation therapy can increase the total dose of radiation that can be delivered safely to the tumour.

GBM is a compact market with most patients managed by specialised centres and clinical trials in GBM are typically modest in size. For these reasons, the company's current strategy is to retain full ownership of TLX101 and develop and commercialise it itself in the US, if approved.

Brain cancer and GBM incidence

According to the National Cancer Institute, brain and central nervous system (CNC) cancer is expected to account for 23,900 new cases and 16,800 deaths in the US in 2018. Globocan predicts that in 2020 there will be 300,400 cases and 225,900 deaths from brain and CNS cancer worldwide, while in the EU in that year there is predicted to be 46,700 new cases and 36,300 deaths. The prognosis is poor regardless of the stage at diagnosis, with an overall five-year survival rate of only 33.2%.

GBM is the most common and most aggressive primary malignant tumour of the brain and spinal cord. Approximately 11,000 patients are diagnosed with GBM each year in the US, representing 46% of all brain and CNS cancers. GBM tumours are characterised by invasive and diffuse growth, which makes complete surgical removal difficult. Standard treatment for GBM entails maximal surgical resection of the tumour followed by radiotherapy with concurrent chemotherapy with temozolomide followed by adjuvant chemotherapy with the same drug to treat the residual infiltrative component of the tumour. Despite this aggressive treatment, the disease invariably returns resulting in a five-year survival rate of only 5%.[28] Options for treating recurrent GBM include bevacizumab (Avastin), alternating electric field therapy (Optune), surgery and EBT[29]. Improved treatments are urgently needed.

Sensitivities

Telix is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that TLX250 and TLX591 will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. While Telix is commencing commercialisation of TLX591-CDx, it is still mainly a mid-stage drug developer, therefore in the foreseeable future most value creation will depend on successful R&D progress and any potential partnering activities, although the timing of licensing deals is typically difficult to forecast. If the FDA requires Telix to conduct a prospective clinical study of TLX591-CDx rather than a blinded review of existing scans, then that could delay filing for full marketing approval by one to two years. Predicting utilisation of PSMA-PET imaging such as TLX591-CDx in prostate cancer is challenging; we model a scenario where it is used as a second-line test when metastases cannot by detected by CT or MRI scans,

28 CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Ostrom et al *Neuro-Oncology* 17:iv1–iv62, 2015

29 https://www.cancer.net/cancer-types/brain-tumor/treatment-options

but if it becomes a first line test in prostate cancer patients with biochemical relapse, or if patients typically undergo repeated PET scans, the market could be significantly larger.

Valuation

Our initial valuation of Telix is A$303m based on a risk-adjusted discounted cash flow model, which includes our estimates of the future milestone payments and royalty streams for TLX250 and TLX591, plus profits from commercialisation of TLX250-CDx, TLX591-CDx and TLX101, as listed in Exhibit 8. We have extended our cash flow forecasts out to 2037 (supported by 12 years of biologicals market exclusivity in the US and 10 years in Europe) but have not included any terminal valuation. We assume a long-term exchange rate of US$0.76/A$ and apply a 12.5% discount rate. We assume that the Atlab acquisition completes as expected in Q318 and that the US$10m consideration is paid through that issue of 20.5m Telix shares. Our valuation is equal to A$1.39 per share on an undiluted basis but including the Atlab acquisition shares and A$1.36/share after diluting for the 10.6m options on issue (exercise price 85c; all of the options would be in the money if the stock was trading in line with our valuation).

We estimate that the current list price of the prostate cancer therapeutic radiopharmaceutical Xofigo in the US is US$91,000 for a course of six injections, as we explain on page 16. Allowing for discounts and rebates, we assume that the net sales price of Telix's MTR therapeutics is US$70,000 per patient in the US, with a 30% discount applying in other markets.

Exhibit 8 shows our market assumptions for TLX250, TLX591 and TLX101 imaging and therapeutic product (TLX101 therapeutic only) and the rNPV for each product. We have offset the risk-adjusted trial cost against revenue for each indication.

Exhibit 8: Telix sum-of-the-parts DCF

	Base case likelihood (%)	rNPV (A$m)	rNPV/sh (A$)	Assumptions
TLX250-CDx kidney cancer imaging	75%	47.4	$0.22	Global peak sales of US$70m. For the US assumes 65,300 kidney cancer cases/yr, 50% candidates for imaging, 25% penetration; for the EU assumes 93,000 cases/yr, 50% candidates for imaging, 20% penetration; pricing US$3,500 per patient, 30% discount in Europe; launch 2021; assume profit margin after deducting royalty to Wilex equal to 30% of net sales. R&D cost: A$12m to compete Phase III.
TLX250 kidney cancer therapeutic	20%	48.9	$0.22	Global peak sales of US$470m. For the US assumes 65,300 kidney cancer cases/yr, 20% eligible for treatment, 20% penetration; for the EU assumes 93,000 cases/yr, 20% eligible, 16% penetration; pricing US$70k per patient, 30% discount in Europe; launch 2024 - biologicals market exclusivity to 2036 in US, 2034 in Europe; assume receives 12% net royalty. R&D cost: A$4m for two small company funded Phase II studies, then out-license.
TLX591-CDx prostate cancer imaging	80%	55.4	$0.25	US peak sales of US$80m assuming 165,000 new cases/yr, 75% candidates for imaging; 15% penetration; revenue to the Kyzeo JV US$3,500 per test; commercial launch as investigational test 2018, FDA approval 2020; assume Telix profit share equal to 20% of JV net sales. R&D cost: US$2m for a Phase III study based on re-read of existing scans.
TLX591 prostate cancer therapeutic	20%	101.7	$0.47	Global peak sales of US$1,080m. For the US assumes 29,400 deaths/yr, 90% eligible for treatment, 15% penetration; for the EU assumes 84,000 deaths/yr, 90% eligible 12% penetration; pricing US$70k per patient, 30% discount in Europe; launch 2025 - biologicals market exclusivity to 2037 in US, 2035 in Europe; assume receives 12% net royalty. R&D cost: A$20m for Phase II, then out-license.
TLX101 brain cancer therapeutic	10%	35.8	$0.16	Global peak sales of US$530m assuming annual US incidence of GBM of 11,000 cases, 90% eligible for therapy, 25% penetration; EU GBM incidence 21,500, 90% eligible, 15% penetration; pricing US$70k per patient, 30% discount in Europe; launch 2025; 15% royalty on net sales. R&D cost: A$6m for Phase I/II, A$25m for Phase III.
SG&A to 2024		-28.6	-$0.13	
Portfolio total		**260.7**	**$1.20**	
Cash (30 June 2018)		42.0	$0.19	
Enterprise total		**302.7**	**$1.39**	

Source: Edison Investment Research. Note: NPV adjusted for tax at an effective tax rate of 25%. We assume that the addressable markets grow at 3% per year. We show our estimate of net royalty rate or profit margin after deducting estimated trailing royalties to IP holders. We have included an assumed 20.5m shares for the expected acquisition of Atlab (see page 3).

Deal terms are based on relevant benchmarks over the last few years (sourced from EvaluatePharma and the industry group BIO). There are few directly comparable deals, ie mid-stage, MTR therapeutics and imaging agents for cancer. Therefore, we looked firstly at deal terms within the targeted therapy space, which included average upfront/milestones of US$127m/US$788m (Exhibit 9). Additionally, based on data in a report produced by BIO, we calculated that among 124 global licencing deals for Phase II therapeutics from 2013 to 2017 (for all diseases) the average upfront/milestones were US$46m/US$281m. Averaging these two data sources, we assume upfront/milestones of US$86m/US$535m for a licence deal for Telix's product pipeline. We assume half of those milestone payments (US$268m) are for clinical and regulatory milestones and half are sales-based milestones. We split the US$86m upfront and US$268m clinical and regulatory milestones between the TLX250 kidney cancer therapeutic and the TLX591 prostate cancer therapeutic, adjusted with a 20-70% probability and weighted according to peak sales.

We do not include the potential sales-based milestones in our forecasts, and instead model a 15% royalty rate for the Phase II products (Exhibit 8, above, shows our assumed net royalty due to Telix after deducting trailing royalties).

Exhibit 9: Comparable Phase I/II oncology deals targeting solid tumours

Date	Licensor	Licensee	Product	Pharmacological class / Target	Indications included in the deal	Upfront (US$m)	Deal value (excl. upfront) (US$m)
Radiotherapeutics							
3/9/2009	Bayer	Algeta	Xofigo (alpharadin)	^{223}Radium	Prostate cancer	61	740
Targeted antibodies							
10/02/2017	Immunomedics	Seattle Genetics	Govitecan (IMMU-132)	TROP-2	TROP-2 expressing solid tumours (eg breast, lung, bladder)	300	1,757
15/10/2015	Five Prime Therapeutics	Bristol-Myers Squibb	CSF1R antibody (FPA008) in combination with Opdivo	CSF1R	Six undisclosed solid tumours	350	1,390
03/12/2013	Oncomed Pharmaceuticals	Celgene	Up to six anti-cancer stem cell product candidates (including demcizumab)	DLL4, VEGF	Oncology (including demcizumab for pancreatic cancer)	155	967
06/09/2012	Symphogen	Merck KGaA	SYM004	EGFR (Mab)	All indications (including colorectal and head and neck cancer)	25	597
21/03/2011	Five Prime Therapeutics	Human Genome Sciences	FP-1039	FGFR1	Multiple tumor types; endometrial cancer Phase II underway.	50	445
Small molecules							
14/11/2017	Loxo Oncology	Bayer	Larotrectinib and LOXO-195	TRK	TRK fusion cancers (eg. lung)	400	1,150
28/07/2015	Hanmi Pharmaceutical	Boehringer Ingelheim	Olmutinib	EGFR (TKI)	EGFR mutation positive lung cancer	50	680
15/12/2014	Geron	Johnson & Johnson	Imetelstat	Telomerase inhibitor	Oncology including haematological malignancies and other therapeutic uses	35	900
1/11/2013	Nerviano	Ignyta	RXDX-101 & RXDX-102	TrK, ROS1 and ALK (TKI)	Solid tumours	6	105
08/12/2011	Pharmacyclics	Johnson & Johnson	PCI-32765	BTK inhibitor	B-cell malignancies, solid tumours, immune disorders	150	825
02/02/2010	Topotarget	Spectrum Pharmaceuticals	Belinostat	HDAC inhibitor	Haematological cancers, solid tumours	30	320
28/04/2009	Ardea Bioscience	Bayer	RDEA119	MEK inhibitor	Solid tumours	35	372

Source: Edison Investment Research, EvaluatePharma, BioCentury, company press releases.

Financials

Telix was incorporated on 3 January 2017 and reported an operating loss for the year ending 31 December 2017 of A$6.4m. Expenses associated with R&D projects were A$3.0m, personnel expenses were A$1.3m and administration and consulting costs totalled A$2.3m. Our total operating loss estimates for 2018, 2019 and 2020 grow to A$13.0m, $17.9m and $15.8m, respectively, mainly due to increased R&D expenditure (detailed in Exhibit 8) as Telix ramps up its clinical trial programme, partly offset by the Australian government's R&D rebate scheme. Telix has received an advance/overseas R&D tax finding totalling A$55.2m regarding the eligibility for the R&D rebate of overseas R&D expenditure that is essential to Telix's programmes but cannot be executed in Australia by Australian vendors and service providers.

Telix had A$42.0m cash and equivalents at 30 June 2018 as compared to A$48.7m at the beginning of 2018. Although Telix has substantial cash reserves and is funded into 2020, we estimate that it may need additional funding of A$4m in 2020, which we include as indicative long-term debt. The actual funding requirement (if any) will depend on the rate of R&D expenditure and the timing of licensing transaction. Our estimated funding requirement is based on our assumption that Telix out-licences, TLX-250 and TLX591 in a single transaction in 2021 by which time the results of a Phase II study of TLX591 in prostate cancer are expected to be known. However, if it enters a licensing transaction in 2020 it may not need any additional funding.

Exhibit 10: Financial summary

A$'000s	2017	2018e	2019e	2020e
Year end 31 December	AASB	AASB	AASB	AASB
PROFIT & LOSS				
Sales, royalties, milestones	0	0	151	622
Other (includes R&D tax rebate)	403	5,000	8,206	6,012
Revenue	403	5,000	8,357	6,634
R&D expenses	(2,977)	(12,000)	(20,000)	(16,000)
SG&A expenses	(3,538)	(6,049)	(6,229)	(6,419)
Other	(291)	0	0	0
EBITDA	(6,403)	(13,049)	(17,872)	(15,785)
Operating Profit (before GW and except.)	(6,403)	(13,049)	(17,893)	(15,821)
Intangible Amortisation	(4)	(151)	(136)	(122)
Exceptionals	0	0	0	0
Operating Profit	(6,407)	(13,200)	(18,029)	(15,944)
Net Interest	30	488	317	97
Profit Before Tax (norm)	(6,377)	(12,712)	(17,712)	(15,846)
Profit Before Tax (reported)	(6,377)	(12,712)	(17,712)	(15,846)
Tax benefit	0	0	0	0
Profit After Tax (norm)	(6,377)	(12,712)	(17,712)	(15,846)
Profit After Tax (reported)	(6,377)	(12,712)	(17,712)	(15,846)
Average Number of Shares Outstanding (m)	128.0	207.7	217.9	217.9
EPS - normalised (c)	(4.98)	(6.12)	(8.13)	(7.27)
EPS - diluted (c)	(4.98)	(6.12)	(8.13)	(7.27)
Dividend per share (A$)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	1,549	9,295	9,238	9,179
Intangible Assets	1,508	1,357	1,222	1,099
Tangible Assets	5	105	184	247
Investments	35	7,832	7,832	7,832
Current Assets	49,545	36,883	18,113	6,349
Stocks	0	0	0	0
Debtors	339	4,735	7,935	5,735
Cash	48,759	31,701	9,730	166
Other	447	447	447	447
Current Liabilities	(1,468)	(1,468)	(353)	(377)
Creditors	(1,123)	(1,123)	(8)	(31)
Short term borrowings	(345)	(345)	(345)	(345)
Other	0	0	0	0
Long Term Liabilities	(332)	(332)	(332)	(4,332)
Long term borrowings	0	0	0	(4,000)
Other long term liabilities	(332)	(332)	(332)	(332)
Net Assets	49,293	44,377	26,665	10,819
CASH FLOW				
Operating Cash Flow	(6,060)	(17,446)	(22,188)	(13,561)
Net Interest	29	488	317	97
Tax	0	0	0	0
Capex	(6)	(100)	(100)	(100)
Acquisitions/disposals	4	0	0	0
Equity Financing	55,561	0	0	0
Dividends	0	0	0	0
Other	0	0	0	0
Net Cash Flow	49,528	(17,058)	(21,971)	(13,564)
Opening net debt/(cash)	1,115	(48,414)	(31,355)	(9,385)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(48,414)	(31,355)	(9,385)	4,179

Source: Edison Investment Research, Telix Pharmaceuticals accounts

Contact details	Revenue by geography
401/55 Flemington Road North Melbourne, VIC, 3006 Australia info@telixpharma.com www.telixpharma.com	N/A

Board and Management

CEO and managing director: Christian Behrenbruch	Chairman: Kevin McCann
Dr Christian Behrenbruch has 20 years of healthcare entrepreneurship and executive leadership experience. He has previously served in a CEO or executive director capacity at Mirada Solutions, CTI Molecular Imaging (now Siemens Healthcare), Fibron Technologies and ImaginAb. Christian holds a D.Phil (PhD) in biomedical engineering from the University of Oxford, an executive MBA jointly awarded from New York University, HEC Paris and the London School of Economics (TRIUM Programme) and a Juris Doctor (Law) from the University of Melbourne.	Mr Kevin McCann is chairman of Citadel Group (ASX: CGL) and the Sydney Harbour Federation Trust. He is a member of the Male Champions of Change, a Pro Chancellor and Fellow of the Senate of the University of Sydney, co-vice chair of the New Colombo Plan Reference Group, a director of the US Studies Centre, director and member of the Advisory Board of Evans and Partners and chair of the National Library of Australia Foundation. In the previous three years, Kevin has been chairman of Macquarie Group (ASX: MQG) and Macquarie Bank (ASX: MBL).
Executive director and chief medical officer: Andreas Kluge	
Dr Andreas Kluge has 20 years of clinical research and development experience, including as founder, general manager and medical director for ABX CRO, a full service CRO for Phase I-III biological, radiopharmaceutical and anticancer trials based in Dresden, Germany. He is also founder and was founding CEO of ABX GmbH (www.abx.de), one of the leading manufacturers of radiopharmaceutical precursors globally. Andreas is further founder, general manager and medical director for Therapeia, an early-stage development company in the field of neuro-oncology, which was acquired by Telix. Andreas has extensive experience in the practice of nuclear medicine and radiochemistry, molecular imaging and the clinical development of novel radionuclide-based products and devices.	

Principal shareholders	(%)
Gnosis	12.5
Elk River Holdings Pty Ltd as trustee for The Behrenbruch Family Trust	12.5
FIL Investment Management (Hong Kong)	10.0
Acorn Capital	5.6

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