PITT STREET RESEARCH

Race Oncology Limited

Precision oncology & chemotherapy cardioprotection

Share Price: A$2.35

ASX: RAC

Sector: Pharmaceuticals & Life Sciences

17 October 2022

Race Oncology Limited (ASX:RAC) is an Australian pharmaceutical company focused on the development of its key drug, Zantrene, which is currently being studied for pre-clinical and clinical efficacy in several cancer indications. Zantrene is a highly targeted precision oncology agent as well as a chemotherapy cardioprotective. The drug is the most potent small molecule inhibitor of the key epitransgenomic Fatso/Fat mass and obesity-associated (FTO) protein.

Zantrene's dual blockbuster potential

The market opportunity for Zantrene is large with the global FTO addressable cancer market estimated to be more than US$120bn in 2020. RAC expects to generate oncology revenues from: (a) FTO-driven cancers including acute myeloid leukaemia (AML), melanoma, renal cancer, breast and pancreatic, and colorectal cancers; and (b) Protection from anthracycline and proteasome inhibitor cardiac damage which is an independent multi-billion dollar opportunity. Notably, in pre-clinical models Zantrene protects the heart from anthracycline and proteasome inhibitor induced damage while providing improved anti-cancer treatments. We believe this is an unmatched differentiator for the company.

Success in AML is likely to drive growth in near term

RAC has completed a Phase II single agent clinical trial pertaining to the use of Zantrene in treating relapsed/refractory AML and is currently in another two Phase I/II trials exploring combination treatment in AML as well as treatment of extra-medullary AML. Furthermore, it is in the process of preparing to file an Investigational New Drug application in the US (US IND) for extramedullary AML, besides owning an orphan drug designation for the treatment of AML in the US. We think that success in the AML field will be a springboard for the company to support its other growth pillars, viz., cardioprotection (breast and other cancers), melanoma and renal cancer programmes.

Valuation range of A$6.61-A$11.91 per share

We value RAC at A$3.4bn base case and A$6.1bn bull case. Adjusting for probability and accounting for future capital raises, this equates to A$6.61 per share base case and A$11.91 per share bull case. We have used a DCF approach assuming Zantrene is commercialised according to forecasted timelines. Commercialisation could occur either by RAC or a potential partner that would acquire Zantrene and/or RAC. Key risks to our model include clinical, regulatory, commercial and competition risks. See page 18 for an outline of these risks.

Market cap. (A$ m)	374.6
# shares outstanding (m)	159.4
# shares fully diluted (m)	173.2
Market cap ful. dil. (A$ m)	407.0
Free float	86.4%
12-months high/low (A$)	3.77 / 1.50
Avg. 12M daily volume ('1000)	222.4
Website	www.raceoncology.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)

Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A$)	6.61-11.91
WACC	11.37%
Assumed terminal growth rate	2.0%

Source: Pitt Street Research

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Introducing Race Oncology, ASX: RAC

RAC is a precision oncology company focussed on the development of the Phase II/III drug Zantrene

Race Oncology Limited (ASX:RAC) is a pharmaceutical company based in Australia that is focussed on the investigation and development of its key drug, Zantrene® (bisantrene dihydrochloride).

Based on recent independent research, Zantrene is the most potent known small molecule inhibitor of the Fatso/Fat mass and obesity-associated (FTO1) protein, inhibition of which is helpful in killing or slowing the growth of a wide range of cancers. The company will be initially focusing on the treatment of a few specific cancer indications as proof-of-concept – acute myeloid leukaemia (AML), melanoma, clear cell renal cell carcinoma (ccRCC; a kidney cancer) and breast cancer. Zantrene has already shown pre-clinical and clinical efficacy as a (1) low dose, precision oncology agent; and (2) cardioprotective chemotherapeutic. Furthermore, RAC has been granted an orphan drug designation in the US for the treatment of AML – providing it seven years of post-approval market exclusivity in the US from the date of FDA approval. RAC currently owns six granted US patents on Zantrene.

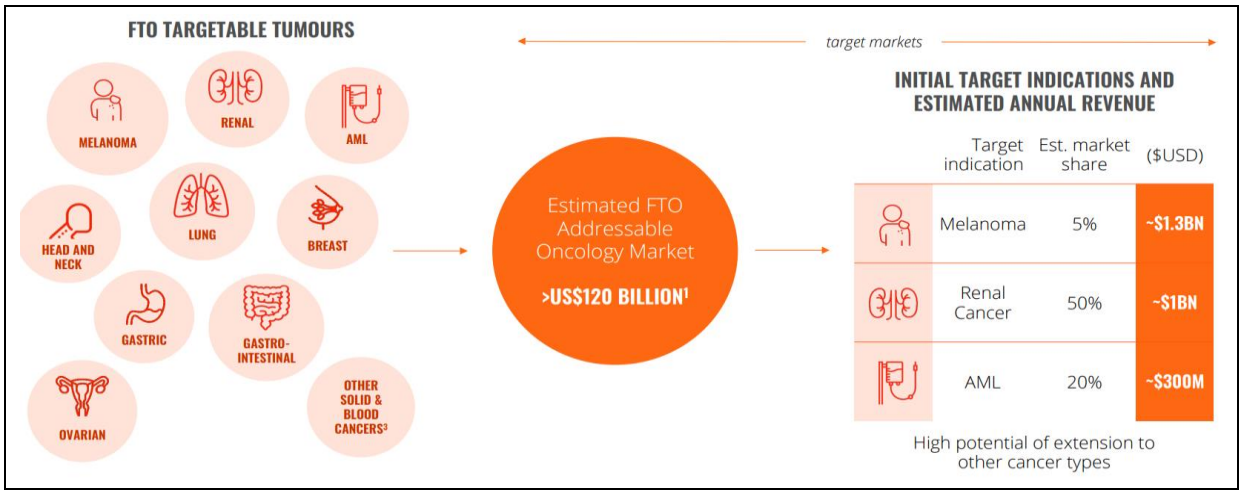
The market potential for Zantrene is huge

RAC expects a multi-billion market for Zantrene in three targeted cancer indications alone

According to Research and Markets, the global oncology drugs market is expected to grow at a CAGR of 7.5% during 2020–2030 to reach US$274bn. This is expected to be driven by a rise in the incidence of various cancer indications, increase in cancer awareness, early detection of the disease, growing availability of drugs and uptick in elderly population. More specifically, the global FTO addressable oncology market is over US$120bn (based on EvaluatePharma and Infinium Research), and we expect it to grow at a pace similar to the broader market. We have discussed the commercial market potential for Zantrene below:

- **Potential from proof-of-concept FTO targeted cancer indications:** RAC conservatively expects annual oncology revenues of >US$2.6bn from just three proof-of-concept targeted cancer indications – AML, melanoma and renal cancer (Figure 1). This is based on the company's estimated peak market share of 20%, 50% and 5% in AML, renal cancer AND melanoma markets, respectively.

Figure 1: FTO and Cancer – Broad commercial potential



Source: Company

[1] FTO was originally identified in the 1990s in a natural mutant mouse and was found to cause a fused toe phenotype. The region lost in the mouse contained 5 gene, and the largest gene was given the name Fused Toe O (FTO).

- **Potential from other FTO-driven cancers:** RAC also aims to tap the market of other FTO-driven cancers. For instance, RAC has successfully pursued pre-clinical studies to test Zantrene's ability to treat breast cancer (US$26bn market globally) and pancreatic/colorectal cancer (US$21.2bn market) via targeting the FTO protein. Via the use of biomarker based approval this could be extended to all cancers that overexpress FTO.
- **Potential from cardioprotective properties of Zantrene:** This could be a major breakthrough in the cancer therapy market, with anthracyclines being widely used in various treatments today. While the lower cardiotoxicity of Zantrene was known for several years, recent pre-clinical studies have shown that Zantrene is able to protect the heart from proteasome inhibitor and anthracycline induced damage while also improving anti-cancer efficacy. This effect is independent of FTO inhibition and opens up a significant secondary opportunity for Zantrene as it could be used as a combination therapy for most patients where anthracyclines or proteasome inhibitors are indicated.

Zantrene's edge and RAC's three-pillar growth strategy

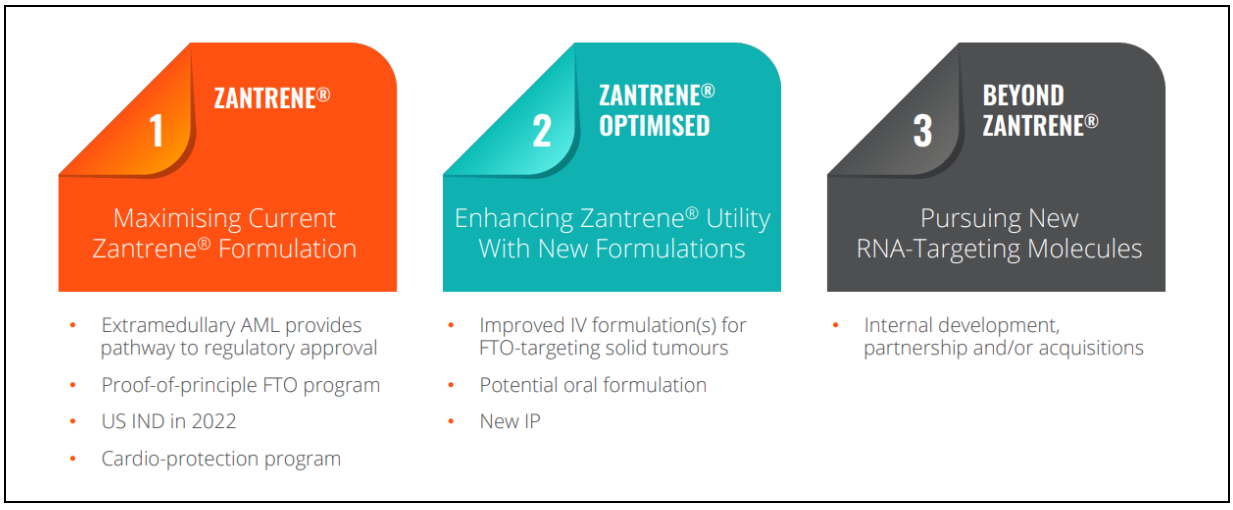
Zantrene holds an edge over other cancer treatments in three ways:

- Possessing extensive prior clinical history in more than 50 clinical trials and 1500 patients. Shown to have activity in a range of cancers despite being used sub-optimally.
- It has been recognised as the most potent enzymatic inhibitor of the FTO protein, clearly outpacing other FTO inhibitor drugs such as Dac51 and Saikosaponin D, both currently in pre-clinical development stages.
- In pre-clinical studies it offers a two-fold benefit – (1) it acts as an effective anti-cancer agent by inhibiting FTO protein, thereby slowing down cancer growth; and (2) prevents development of cardiovascular damage by protecting against the toxic effects on the heart from the most widely used chemotherapy agents, including doxorubicin.

Zantrene has been identified as the most potent small molecule inhibitor of FTO protein and prevents the heart from the toxic effects of chemotherapy agents

RAC aims to capitalise on the commercial opportunity in cancer and cardioprotection provided by Zantrene, and is currently pursuing a three-pillar strategy (Figure 2) to achieve it.

Figure 2: RAC's three-pillar strategy



Source: Company

- **First Pillar "Zantrene"**: Involves maximising the current Zantrene formulation across relapsed/refractory AML, extramedullary AML (EMD AML), and cardioprotection (breast and other cancers). This pillar offers a rapid route to regulatory approval under the FDA 505(b)(2) pathway enabling leverage of extensive clinical and preclinical history of the drug.
- **Second pillar "Zantrene Optimised":** Involves the development of new formulations for Zantrene allowing greater IP protection and extending its application to FTO-driven solid tumours such as melanoma and kidney cancer.
- **Third pillar "Beyond Zantrene":** Focussing on new molecular development to target FTO and other m^6A RNA regulator proteins that will allow addressing non-cancer indications.

Ten reasons to consider Race Oncology

1) **RAC has the leading drug in the exciting new epitranscriptomics field with FTO targeting properties** – Zantrene has recently been noted as the first-in-class and best-in-class inhibitor of the FTO protein allowing RAC to target multiple types of cancer such as AML, breast cancer, pancreatic cancer and skin cancer. RAC has the potential to secure the leading position in the FTO-inhibitor cancer therapy market. Other drugs in this space (such as Dac51 and Saikosaponin) are years away from human clinical trials.
2) **Zantrene is in the clinic for multiple cancer indications** – RAC has made solid progress with Zantrene with the drug already proven successful in Phase II clinical trials to treat AML cancers. We expect the company to start generating revenue from the drug in the medium term. Moreover, it holds an FDA orphan drug designation to treat AML, giving it seven years of post-approval market exclusivity.
3) **Cardioprotection is new opportunity with huge potential** – With millions of patients taking anthracyclines each year and many suffering from heart damage as a side effect, the existing market for cardioprotection with improved anti-cancer treatment is substantial. Zantrene's cardioprotective abilities, while being synergistic with chemotherapy drugs, offers RAC a large commercial opportunity with high potential to improve modern chemotherapy.
4) **Capability to offer combination treatment for cancer** – Zantrene is one of the few chemotherapeutic agents with immunostimulatory properties. This aspect of the drug not only increases its potential efficacy but also opens the doors for RAC to investigate its drug's synergies with other immune oncology agents. Recent preclinical studies by RAC have shown that Zantrene is able to overcome immune therapy resistance. Given the wide use of immune therapies, we think this is likely to lead to multiple successful combinatorial therapies targeting various cancers.
5) **Potential to target multiple types of cancers** – The company has started exploring the utility of Zantrene in other FTO-driven cancers, such as breast cancer, lung cancer, colorectal and pancreatic cancer. The positive preclinical results indicate the potential of the drug to generate multiple revenue streams (including recurring revenue) post commercialisation.
6) **Robust business strategy** – RAC's three-pillar business strategy is designed to recognise and leverage Zantrene's value as an FTO inhibitor as well as a cardioprotective chemotherapeutic. It is aimed at enhancing

partnering, licensing or sale opportunities via advancing Zantrene in preclinical and clinical trials across a range of cancer indications in the medium term, as well as developing new ribonucleic acid (RNA) regulating molecules in the long term.

7) **Targeting new pathways** – RAC is no longer a single product company that is targeting a single application. Besides exploring Zantrene's use in a range of solid tumours, RAC has started developing new molecules and formulations which will (a) allow oral administration of an FTO inhibitor; (b) target other m^6A RNA regulator proteins; and (c) address non-cancer indications. We believe this will offer new opportunities with significant commercial potential.
8) **Growing intellectual property (IP) portfolio** – RAC has a rich IP portfolio with six US patents on Zantrene for use in cancer and related analogues, 13 provisional patents covering use in combination with other drugs under the melanoma and ccRCC patent family, and one provisional patent covering use to prevent chemotherapy heart damage. Further, the company has two pending patents related to manufacture and formulation of Zantrene to modern FDA standards.
9) **Experienced management with skin in the game** – RAC has a solid management team that has extensive experience in building and managing successful healthcare businesses. Its Managing Director and CEO, Phillip R Lynch, has supported J&J in the APAC region for over 30 years and has diverse experience across corporate development, strategy, financial performance, M&A, marketing and governance. The company's management team also include oncology specialists such as Dr David Fuller, Professor Michael Kelso and Dr. Marinella Messina. Further, RAC's Chief Scientific Officer and Executive Director, Dr. Daniel Tillett, is its largest shareholder (8.5% share) which should provide confidence to investors.
10) **We believe the business is highly undervalued based on the current market price,** and investors are not factoring in the full potential of the company's key pipeline programmes. We expect the stock to be re-rated toward our valuation range on the back of successful Phase II & III clinical data and US IND approval for AML indications, and encouraging preclinical and clinical data for other cancer types such as melanoma and renal cancer.

Importance of Zantrene in cancer treatment

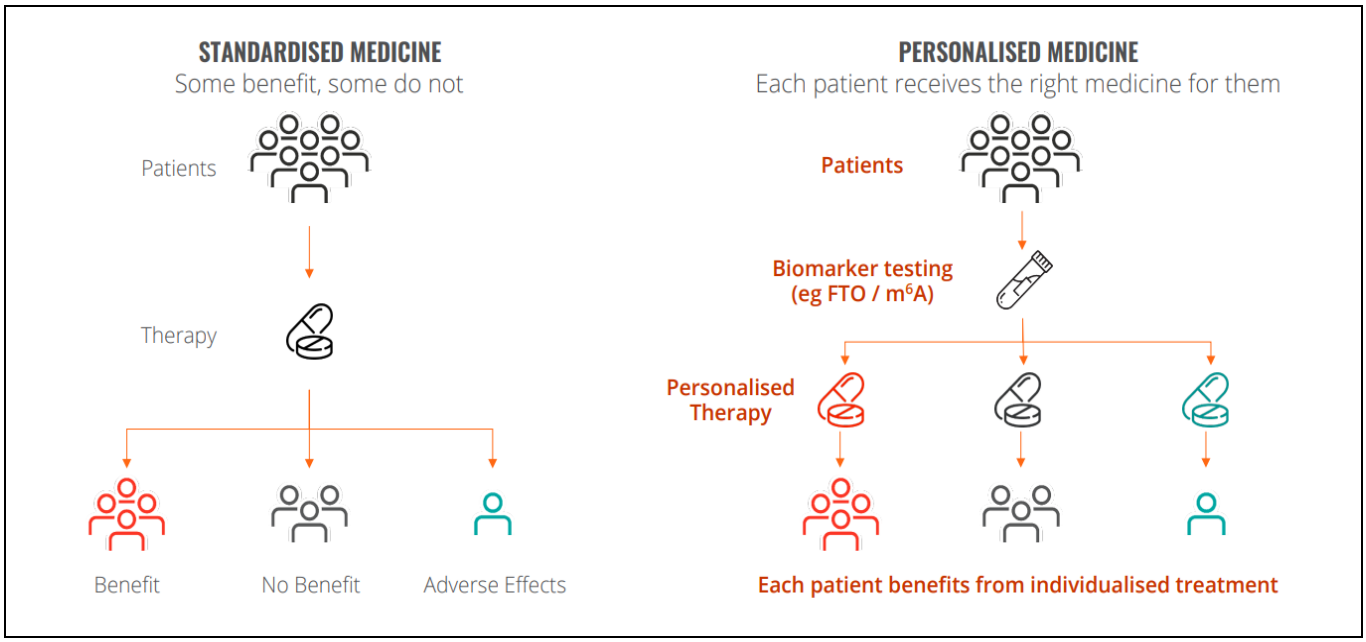
Zantrene is a small-molecule anthracene-derivative that has shown to possess a tolerable clinical safety profile and therapeutic activity in multiple cancer indications, including leukaemia, melanoma, ovarian cancer and breast cancer.

RAC has been exploring the use of Zantrene as a new therapy for AML, melanoma ccRCC (kidney cancer) and breast cancer, which are all frequent FTO protein-driven cancers. Zantrene holds immense potential as a precision oncology agent (Figure 3) targeting multiple cancer indications with an estimated annual oncology revenue of >US$2.6bn.

The two major reasons that offer Zantrene an edge over other existing cancer treatments include:

– It is the most potent known enzymatic inhibitor of FTO protein.
– Although it is similar to anthracyclines (doxorubicin[2]) in activity, it has been shown clinically to have less cardiotoxicity.

Figure 3: Standardised medicine vs. Zantrene (personalised medicine)



Source: Company

History of Zantrene over the years

Anthracyclines were first acknowledged in the mid-1960s as notable anti-cancer drugs due to their anti-tumour properties. The two major drugs discovered at the time that could successfully make it to the market were daunorubicin and doxorubicin but both faced issues regarding cardiotoxicity and development of multidrug resistance. This continued the quest for an anti-cancerous drug with lower cardiotoxicity levels.

– In the 1980s, Lederle Laboratories, a division of the US chemical company American Cyanamid, developed Zantrene (then known as bisantrene) as an anti-tumour anthracycline alternative without the cardiotoxicity and multidrug resistance issues. To develop the drug,

[2] Cancer Res. 1983 Jun; 43(6); 2648-53.

Lederle and the National Cancer Institute are believed to have spent an amount that would be equivalent to US$500m today.

- In 1988, Zantrene received regulatory approval for human medical use in France to target treat AML, following a series of clinical studies in over 1500 patients. However, commercial development of the drug was dropped in the early 1990s, anecdotally understood to be due to a combination of flawed trial design, internal competition from competing oncology drugs, and financial difficulties at Lederle's parent company.
- In 2013, Bill Garner and John Rothman formed Update Pharma to re-develop Zantrene after filing for patent protection. Update Pharma was later acquired and renamed as Race Oncology Ltd. which commenced trading on ASX in July 2016.
- In June 2020, Zantrene was identified independently as the most potent enzymatic inhibitor of FTO. In the same month RAC announced the results of a small AML Phase II trial in Israel which showed a 40% response rate in very heavily pre-treated patients resistant to all other treatment options.
- In March 2021, RAC announced its final breast cancer preclinical results demonstrating Zantrene to be an effective chemotherapeutic agent across a diverse panel of genetically defined breast cancer subtypes.

AML accounts for over 80% of adult leukaemia, which provides a significant market opportunity for bisantrene/ bisantrene-derived products

- In June 2021, RAC roped a global contract research organisation, Parexel, to support Phase I/II Australian trial of EMD AML.
- In May 2022, the company received Research Governance Office (RGO) approval for EMD AML and myelodysplastic syndromes (MDS) human trial. Further, the Zantrene AML trial at Chaim Sheba, Israel, advanced to Phase II.
- In June 2022, the company released the interim results of its preclinical cardioprotection programme exhibiting Zantrene's ability to protect hearts in animal models of chemotherapy damage. RAC also exhibited results of its preclinical studies identifying Zantrene's synergy with protein kinase inhibitors for treating melanoma and kidney cancer and its potential to treat pancreatic and colorectal cancers.

Zantrene offers potential treatment options for multiple cancers

Supportive results from multiple cancer-based studies are a positive sign for Zantrene's commercialisation plans

Zantrene has been explored as a treatment for many cancers over the years. The drug has been subjected to numerous clinical studies in over 1,500 patients across various types of cancers, including AML, lymphoma, ovarian and breast cancer. Recent AML clinical and broader pre-clinical data confirm Zantrene against the following:

1) **AML**: Zantrene was extensively explored as a safe and effective treatment for AML. Several clinical trials have been conducted over the years (Tosi et. al., 1989[3]; Spadea et. al., 1993[4]; Leblanc et. al., 1994[5]) to prove its efficacy as an AML treatment. These studies suggest that Zantrene has a great potential to treat relapsed/refractory AML.

2) **Melanoma:** This is regarded as one of the most aggressive cancers. Research[6] shows that FTO is overexpressed in ~50% of all metastatic

[3] Haematologica. 1989 Nov-Dec; 74(6); 555-8.
[4] Leuk Lymphoma. 1993 Feb; 9(3); 217-20.
[5] Med Pediatr Oncol. 1994; 22(2); 119-24.
[6] m^{6}A mRNA demethylase FTO regulates melanoma tumorigenicity and response to anti-PD-1 blockade; Nature Communications; 10(1); 1131–14; Yang, S., Wei, J., Cui, Y.-H., Park, G., Shah, P., Deng, Y., et al. (2019).

melanomas and inhibition of FTO can overcome immune-therapy (checkpoint) resistance. Thus, Zantrene can have significant opportunity in this therapeutic area.

3) **ccRCC kidney cancer:** This is the 10th most common cancer, but with a low survival rate as it is frequently only diagnosed at an advanced stage. About 90% of ccRCC have mutations in von Hippel-Lindau (VHL) tumour suppressor gene[7]. In cancers with mutated VHL genes, inhibition of FTO has been found to kill ccRCC cancers[8].

4) **Breast cancer:** In March 2021, RAC published final results from its collaborative preclinical research programme with the University of Newcastle and Hunter Medical Research Institute, highlighting Zantrene's ability to be an effective chemotherapeutic agent across a diverse panel of genetically defined breast cancer subtypes and to also kill breast cancer cells resistant to a wide range of breast cancer treatment drugs. According to the Breast Cancer Research Foundation (BCRF), more than 2.3 million women worldwide were diagnosed with breast cancer in 2020, and the drug market was valued at US$26bn (2021) globally.

5) **Pancreatic and colorectal cancers:** In June 2022, RAC published novel preclinical data highlighting Zantrene's potential in pancreatic and colorectal cancers. It demonstrated the drug's ability to inhibit FTO and suppress pancreatic carcinogenesis via targeting cancer stem cell maintenance. It also explored the use of the drug as an adjunctive treatment to overcome colorectal cancer resistant to 5-FU[9]-based chemotherapy via inhibition of FTO in both cell and mouse models.

We believe that important research programmes support Zantrene's utility in multiple cancer indications which complements RAC's findings that Zantrene can inhibit FTO in AML, melanoma and ccRCC.

Zantrene is an anti-cancer drug with multiple mechanisms of actions

Zantrene has been reported to have multiple mechanisms of action beyond FTO inhibition, including immunologic, cytotoxic, and genomic effects.

As Zantrene inherits the ability to augment the work of immune effector cells, it offers opportunities to develop therapies by combining with immune-oncology agents

1) **Cytotoxic:** Zantrene can intercalates with and disrupts the configuration of DNA, leading to DNA single-strand breaks, DNA-protein crosslinking and inhibition of DNA replication.

2) **Genomic/non-cytotoxic mechanism[10]:** The molecule has the ability to act as a telomerase inhibitor[11] by stabilising certain guanine-rich areas of DNA (called G-quadruplex) which can inhibit the displacement of telomerase binding proteins (provide protection and replication of chromosome ends to prevent degradation).

   Immunologic[12]: It activates tumour-inhibitory macrophages that inhibit the growth of tumour cells. According to a recent study[13],

[7] Analysis of VHL Gene Alterations and their Relationship to Clinical Parameters in Sporadic Conventional Renal Cell Carcinoma; Clinical Cancer Research; 15(24); 7582–7592; Young, A. C., Craven, R. A., Cohen, D., Taylor, C., Booth, C., Harnden, P., et al. (2009).
[8] The m6A RNA demethylase FTO is a HIF-independent synthetic lethal partner with the VHL tumour suppressor; Proceedings of the National Academy of Sciences; 117(35); 21441–21449; Xiao, Y., Thakkar, K. N., Zhao, H., Broughton, J., Li, Y., Seoane, J. A., et al. (2020).
[9] 5-FU stands for 5-fluorouracil which is a cytotoxic chemotherapy medication used to treat multiple cancers (breast, colon, rectum, stomach and pancreas).
[10] Biochem Pharmacol; 2010; 79(12); 1781-90.
[11] Telomerase inhibitors prevent the maintenance of telomere length, leading to eventual apoptosis (cell death). Cancer cells maintain the telomere length for unlimited growth by telomerase reactivation via the telomerase binding proteins.
[12] Cancer Res. 1984 Jun; 44(6); 2363-7.
[13] Int J Cancer Res Ther; 2017; 2(2); 2-10.

multiple administrations of activated macrophages tend to be more effective than a single administration. The macrophage activity of Zantrene make it well suited for incorporation into combinatorial regimens that use cytotoxic and immunogenic agents.

Zantrene – RAC's promising anti-cancer drug

RAC's Zantrene is a small molecule anti-cancer drug that has been identified as the most potent and only clinical stage inhibitor of the FTO protein.

Zantrene – the most potent known inhibitor of FTO

FTO is upregulated in all cancer types and exhibits an essential tumour-promoting role, leading to the increased growth and treatment resistance of cancers

Multiple research studies have identified dysregulation (loss of control) of RNA epigenetics (methylation) as a key reason for cancer development. One of the major proteins controlling this dynamic regulatory system is the FTO protein. Increases in the expression of the FTO protein is linked with both cancer development, metastasis and treatment resistance. As a result, regulation of RNA epigenetics and the inhibition of FTO activity in cells has become one of the most promising new areas of cancer research as it has laid the foundation for discovering potential new treatments for many different types of cancers.

Zantrene has clinical and preclinical efficacy as both a low dose (low IC_{50}[14]), highly targeted precision oncology agent as well as cardio-protective chemotherapeutic. Relative to Zantrene, compounds with IC_{50} >1,000nM are unlikely to be useful drugs in the clinic (Figure 4).

Figure 4: Zantrene (Bisantrene) vs. other FTO inhibitors

Drug	IC_{50} (nM)	Potency[1]	Clinical Data	Indications	Efficacy & Known Side Effects
Bisantrene (CS1)	**142.6**	**1**	**Yes (Phase 3)**	**AML, Breast, Pancreatic, GBM, Skin cancers**	**Leukopenia and myelosuppression at high doses**
Dac51	400	3	No	Colon and melanoma	Preclinical. No safety or tolerability data from human clinical trials
Saikosaponin D	460	3	No	AML	Preclinical. No safety or tolerability data from human clinical trials
Brequinar (CS2)	712.8	5	Yes (Phase 2)	AML	Failed anticancer agent. Failed transplant organ rejection drug. Very immunosuppressive. Variable plasma concentrations
Compound 2	1460	10	No	Dopamine Neurons	IC_{50} value in µM range. Preclinical. No safety or tolerability data from human clinical trials
FB23-2	2600	18	No	AML	IC_{50} value in µM range. Preclinical. No safety or tolerability data from human clinical trials
FTO-04	3400	24	No	GBM Stem cells	IC_{50} value in µM range. Preclinical. No safety or tolerability data from human clinical trials
Entacapone	3500	25	Yes (Approved)	Metabolic cells	IC_{50} value in µM range.
MA/MA2	7000	49	Yes (Approved)	-	IC_{50} value in µM range.
MO-I-500	8700	61	No	TNBC	IC_{50} value in µM range. Preclinical. No safety or tolerability data from human clinical trials

Source: Company

Over-production of the FTO protein has been found to be an important factor in the growth of multiple cancers which has led the company to explore Zantrene as a potential therapy for all FTO-driven cancers, as indicated by the following actions:

– In June 2020, research studies by the City of Hope Hospital, Los Angeles, US, supported by a US National Institutes of Health (NIH) grant identified

[14] IC_{50} refers to half-maximal inhibitory concentration. It indicates how much drug is needed to inhibit a biological process by half, thus providing a measure of potency of the drug.

Zantrene as the most potent enzymatic inhibitor of FTO from a screen of more than 260,000 chemical compounds contained in the NIH National Cancer Institute's chemical library. The research also demonstrated, in both human cell and mouse models, that Zantrene specifically killed FTO overexpressing cancers when used at concentrations far below that known to be toxic in humans.

- In April 2021, this work was further confirmed by a separate lab at the University of Chicago in 2021. The study identified that FTO plays a critical role in the development of skin cancers caused by low-level arsenic exposure (which promotes tumour growth) and that Zantrene-targeted inhibition of FTO limits the growth of these skin cancers in both cell culture and mice.
- The solid tumours, melanoma and ccRCC, both overexpress FTO at high frequency. RAC is currently pursuing pre-clinical studies in both cancer types to demonstrate if Zantrene has utility before moving into proof-of concept Phase I/II clinical trials in one or both cancers.

Zantrene chemotherapeutic cardioprotection – a game changer

Since the 1960s, anthracyclines have been employed as chemotherapeutic agents for the treatment of a wide variety of solid organ tumours and hematologic malignancies, including leukaemia, lymphoma, breast cancer, lung cancer, multiple myeloma and sarcoma.

However, the utility of anthracyclines[15], such as doxorubicin and idarubicin, in treating cancer is limited by a cumulative dose-dependent cardiotoxicity, which can cause irreversible heart failures.

Zantrene was known to have lower-cardiotoxic properties, recent studies by RAC have identified that the drug is able to protect the heart from anthracycline-induced damage while being able to synergise with the anthracyclines to better treat cancer.

Non-cardiotoxic and cardio-protective properties of Zantrene can be a major breakthrough in supporting current cancer therapies

- In June 2022, the company shared interim results from the Zantrene preclinical heart safety research programme (led by eminent cardiotoxicity researchers of the University of Newcastle, Australia). The research identified Zantrene's ability to protect the hearts of mice from the damaging effects of anthracyclines (specifically doxorubicin), even on increasing the chemotherapeutic dose without significant additional toxicity or bone marrow suppression.
- Further, in December 2021, RAC shared additional results to the heart safety research programme, identifying the drug's ability to protect heart muscle cells from carfilzomib[16]-induced cell death while improving the carfilzomib-mediated killing of cancer cells. Zantrene was able to salvage over 30% of carfilzomib-induced human heart cells from death.
- The University of Newcastle-led expanded protection discovery followed RAC's announcement in December 2021, which identified Zantrene's ability to protect against anthracycline-induced heart damage while improving the killing of breast cancer cells.

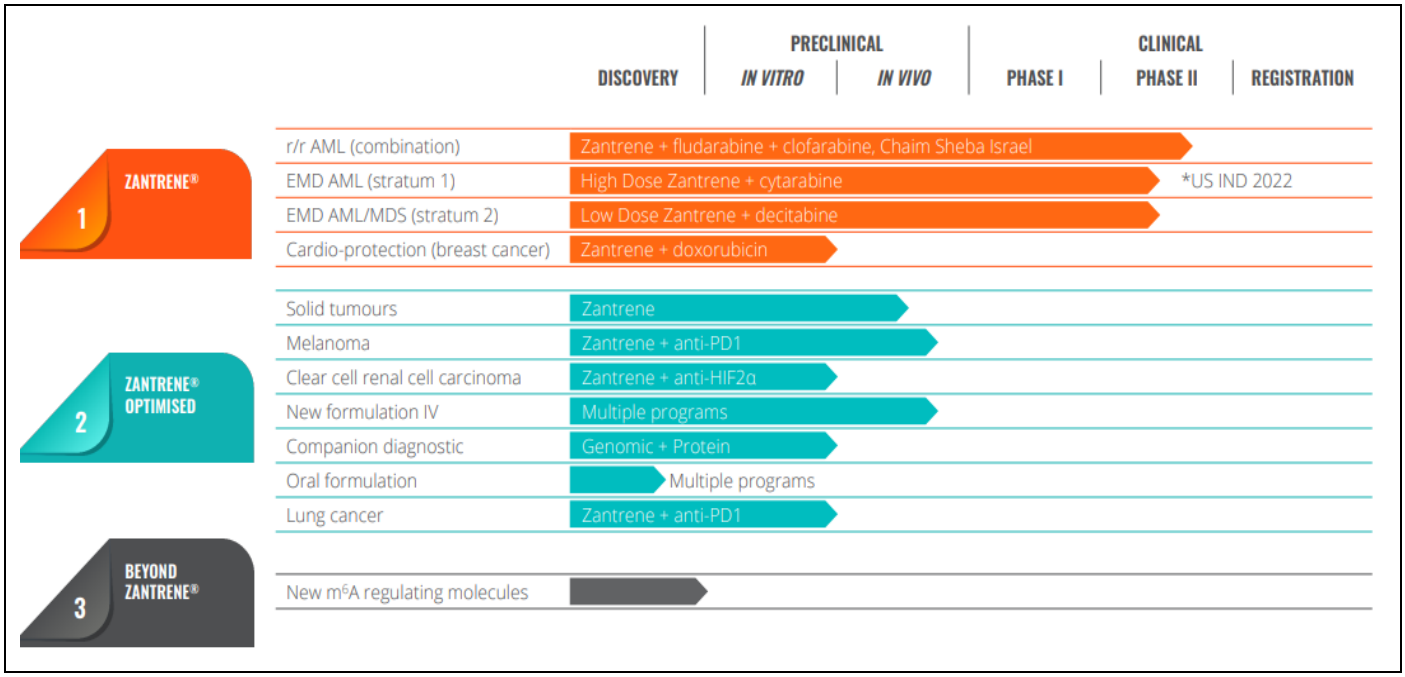
We believe that these recent discoveries open new collaboration opportunities for Zantrene as a potential cardio-protective agent.

[15] Curr Cardiol Rev. 2011 Nov; 7(4); 214-220.
[16] Carfilzomib (trademark Kyprolis) is a highly effective anti-cancer drug used in the treatment of multiple myeloma, but it can cause serious and permanent damage to the heart in many patients.

Growth Pillar 1: AML and cardioprotection

RAC's management is focusing on a three-pillar growth strategy (Figure 5) to systematically leverage the multiple opportunities provided by Zantrene. At present, the most advanced growth pillar for the company are the opportunities in AML and cardioprotection in breast cancer.

Figure 5: RAC's Three-pillar growth strategy



Source: Company

The orphan drug designation for AML provides seven years of post-market approval exclusivity to RAC in the US

AML: AML accounts for ~80% of adult leukaemia and the global AML therapeutics market is estimated at US$587m in the year 2022, and is projected to reach a size of US$976m by 2026 (CAGR of 11%).

- Zantrene has an orphan drug status in the US (conferred by the FDA in February 2014). In January 2018, RAC's key Zantrene patent received a "Notice of Allowance" in the US that provides commercial protection for all uses of Zantrene currently contemplated by RAC in the US (through to 2034). The patent protects the use of Zantrene in patients with refractory or relapsed cancers, including AML and related leukaemia (MDS, acute lymphoblastic leukaemia – ALL, chronic lymphocytic leukaemia – CLL), as well as breast cancer, lymphoma and other types of cancers. Moreover, RAC has been designated as eligible for a Paediatric Priority Review Voucher (PRV) in paediatric AML.
- In June 2020, RAC reported the results of a Phase II single agent trial of Zantrene in heavily pre-treated AML patients. These patients had failed an average of 4 prior lines of treatment. In this very difficult to treat patient group Zantrene achieved an overall response rate of 40%.
- In May 2022, the company's Zantrene AML trial at Chaim Sheba, Israel advanced to Phase II after displaying encouraging clinical responses in heavily pre-treated patients in Phase Ib/II. This trial is aimed at investigating the impact of Zantrene + fludarabine + clofarabine in adult patients with relapsed or refractory AML.

RAC is targeting the FDA 505(b)(2) approval pathway for EMD AML which will save time and money

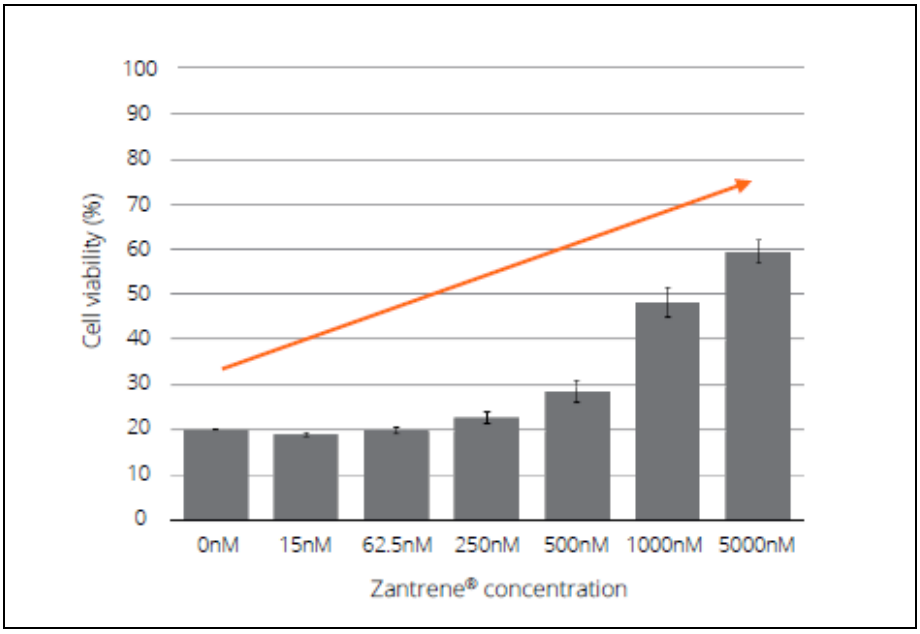
– RAC is particularly focusing on EMD AML as it is an unmet clinical need with poor prognosis and no approved therapies. The company is currently undergoing an open label Phase Ib/IIa clinical trial (BISECT) in patients with EMD AML and MDS. In June 2022, RAC announced the expansion of its FTO-targeted BISECT clinical trial to include five additional trial sites in Spain and Italy and has also signed an agreement with Parexel, to support the additional trial monitoring activities.

  - In May 2022, RAC also received RGO's approval for the human trials of EMD AML and MDS. The open label Phase I trial with a dose expansion Phase II stage will recruit up to 60 patients with EMD AML or MDS at the trial sites in Australia and Europe.
  - The company is targeting filing for US Investigational New Drug (IND) application in 2022. The company was previously advised by the FDA that Zantrene is eligible to be approved under the FDA 505(b)(2) approval pathway for AML. The 505(b)(2) new drug application (NDA) is a streamlined NDA process in which the applicant relies upon one or more investigations conducted by someone other than the applicant and for which the applicant has not obtained right of reference. In essence, the 505(b)(2) pathway enables manufacturers to apply for approval without having to repeat all the drug development work done for an innovator drug. This should enable RAC to utilise the extensive historical clinical data of Zantrene in AML, potentially speeding approval times and lowering development costs.

Cardioprotection (breast and other cancers): The results from multiple research studies suggest Zantrene is an effective anti-cancer agent that can concomitantly provide protection against the irreversible toxic effects on the heart from one of the most commonly used chemotherapy agents, doxorubicin. Zantrene offers the potential to improve health outcomes for many cancer patients and survivors by improving their cancer treatment while preventing development of cardiovascular disease.

RAC's preclinical trial in collaboration with the University of Newcastle clearly supports the proposition that Zantrene protects doxorubicin cardiac damage while improving anti-cancer activity (Figure 6 on page 14). The company has plans to run a Phase IIb clinical trial in breast cancer patients (at serious risk of anthracycline-induced heart damage) in 2022 to clinically explore the cardioprotection potential of its drug.

Figure 6: Zantrene and doxorubicin



Source: Company

Growth Pillar 2: Zantrene Optimised

RAC's management has laid down a robust plan to develop new formulations to extend Zantrene's utility in solid tumours and beyond.

Solid tumours: The company has been constantly investigating Zantrene's application against solid tumours (such as melanoma and ccRCC). It has also been investigating improved IV formulation(s) for FTO-targeting solid tumours. Melanoma and ccRCC both overexpress FTO at high frequency, and RAC is currently pursuing pre-clinical studies in both cancer types to demonstrate if Zantrene has utility before moving into proof-of-concept Phase I/II clinical trials.

Preclinical evidence show potential for rapid translation into clinic for Zantrene Optimised programmes

Melanoma: In March 2021, RAC launched a preclinical study in collaboration with the University of Newcastle, to explore the use of Zantrene as a novel FTO directed treatment for melanoma. In June 2022, the company announced final results of its preclinical study wherein it found that Zantrene in combination with BRAF and MEK[17] protein kinase inhibitors improved the killing of human melanoma cells and better targeted melanoma in organoid and animal tumour models.

In September 2021, the drug was identified to be highly effective at killing a diverse range of melanoma cell subtypes, showing an association between FTO expression levels and melanoma cell sensitivity to Zantrene. These discoveries offer potential non-immunotherapeutic pathways for the use of Zantrene in melanoma treatment.

ccRCC: In March 2022, RAC published final results from its ccRCC preclinical programme, highlighting Zantrene's ability to kill cancer cells independently and in combination with other existing cancer treatments (lenvatinib,

[17] MEK refers to mitogen-activated protein kinase.

cabozantinib and pazopanib). The synergistic combinations have high clinical relevance and potential for rapid translation into the clinic.

Companion diagnostics: Companion diagnostics will help to diagnose patients with FTO using a biomarker as well as monitor treatment response. There are currently two programmes being run by RAC – FTO and global m^6A RNA at the Chaim Sheba hospital and m^6A RNA genomics at University of Newcastle. Both the programmes tackle the issue in different ways, one being a top-down global system and another a bottom-up genomics-based system. Both programmes are complimentary to each other, thus assisting RAC in data collection for developing companion diagnostics.

RAC is trying to reduce the two hour central line infusion line that is currently needed for administering Zantrene

Formulation programme: Current Zantrene formulations require a two-hour central line infusion which makes it a difficult and time consuming administration process. Solid Tumour oncologists typically prefer to deliver drugs in an outpatient setup or in the form of an oral pill that patients can take at home. RAC has been working on a programme for new formulations through its collaboration with the University of Wollongong. The new formulations are aiming for peripheral infusion, shorter infusion time and less frequent administration. Moreover, the new formulations can potentially extend the IP protection around the drug, by effectively resetting the patent clock and offering protection for another 20 years.

Growth Pillar 3: Beyond Zantrene

The third pillar of RAC's strategy, "Beyond Zantrene" is focused on new molecular development and could potentially involve partnerships and acquisitions. The new molecules are expected to (a) allow oral administration of an FTO inhibitor; (b) target other m^6A RNA regulator proteins; and (c) address non-cancer indications – all to extend applications and commercial opportunities beyond Zantrene.

Valuation

We value RAC at A$3.4bn base case and A$6.1bn per share optimistic case, using the DCF approach. Adjusting for probability and accounting for future capital raisings – this equates to a $6.61 base case and $11.91 bull case (Figure 7 on page 17). Our model assumes RAC seeks to commercialise Zantrene in its own right, although it is plausible that it may sell the drug before commercialisation. If the latter scenario eventuates, we think this model could still be useful, pointing towards what a potential transaction might look like.

Market opportunity

- **Market share:** We have considered the potential of the company to capture market share for Zantrene in three ways: (1) In AML and MDS with distinct applications in r/r AML and EMD AML/MDS. (2) As a biomarker licensed therapy targeting FTO overexpression in any cancer type. The average rate for FTO overexpression across all cancers is approximately 15% and we have consequently used 15% in assessing the total market and share RAC could capture. (3) As a chemotherapeutic cardioprotective therapy with improved anti-cancer efficacy. We assume the AML applications are commercialised in FY26 and the others in FY29.
- **Commercialization route:** We assume that RAC would commercialise Zantrene in its own right, seek a sales partnership and pay 50% of the total revenue to the partner. We observe that deals such as these can vary so far as the 'share of the pie' is concerned but there is potential for the smaller partner to capture the bulk of the upside.
- **Commercialization timeline:** We assume that commercialization for the AML indications will be achieved by 2026, while the FTO and cardioprotection indication will be achieved by 2027. We have only considered the US at this stage.

Financials

- **Revenue**: We derive the total revenue for each indication as a product of the number of cases, cost of treatment (in US$), market penetration (%) and (1-partner's share). We assume an 0.675 USD/AUD exchange rate.
- **Expenses**: We assume that once Zantrene is commercialised, it spends a fixed proportion of sales on R&D (20%) and selling, general and administrative expenses (30%). NYU Stern data suggests the industry averages for pharmaceutical companies are 6% and 25% respectively. However, we have assumed a higher proportion for conservatism's sake and also because of the potential of Zantrene beyond Pillar 1. We think a would-be partner in a future transaction would be keen to undertake further R&D work and likely be significantly more resourced to undertake it. As for miscellaneous expenses (such as accounting fees and share registry expenses), we assume 10% annual growth, not expecting it to expand as significantly as the company's sales.
- **Funding & capital raisings**: We assume that over the life of our model, the company will raise a total of $350m in equity. We assume $150m at $3 a share in FY26 and $300m at $4 a share in FY29. This does not impact the enterprise value, but it does decrease the share price. FY26 and FY29 are the points when Zantrene is commercialised against AML

in FY26 and the others in FY29. We think these are reasonable assumptions based on Telix Pharmaceuticals' (ASX: TLX) recent $175m raise which was undertaken just as Illuccix's US commercialisation has begun.

DCF factors

- **Discount rate and terminal value growth rate:** We have used a WACC of 11.37%. This is derived from a risk-free rate of Return of 3.9%, in accordance with the 10-year government bond, a 1.50 beta and a 5.0% equity premium.
- **Probability weighting:** We have discounted our valuation by 50% to account for the lack of certainty of commercialisation.
- **Shares on issue:** As noted above, our shares on issue are post-financing rather than Race's shares on issues at present. Pre-financing, our share price is A$10.79 base case and A$19.40 bull case – still weighted for probability.

Figure 7: DCF valuation for RAC

Valuation (A$)	Base case	Bull case
Present value of FCF	659,614	1,328,713
Present value of Terminal FCF	2,731,689	4,802,590
Enterprise Value	**3,391,303**	**6,131,303**
Net debt (cash)	(33,541)	(33,541)
Equity value (A$)	**3,424,844**	**6,164,844**
Shares outstanding (post financing)	258,911	258,911
Implied price (A$)	**13.23**	**32.81**
Discount factor	**0.50**	**0.50**
Price post-discount	**6.61**	**11.91**
Adjusted Current price (A$ cents)	2.35	2.35
Upside (%)	*181.2%*	*406.9%*

Source: Pitt Street Research

Figure 8: DCF value in A$ using various WACCs

Sensitivity Analysis						
WACC	**11.37%**					
Terminal Growth Rate	**2.00%**					
Implied Price (A$ cents)	**6.61**	*8.4%*	*10.4%*	*11.4%*	*12.4%*	*14.4%*
	1.00%	10.33	7.14	6.06	5.19	3.91
	1.50%	11.01	7.49	6.32	5.39	4.03
	2.00%	11.79	7.84	**6.61**	5.61	4.17
	2.50%	12.71	8.33	6.94	5.86	4.31
	3.00%	13.80	8.83	7.30	6.13	4.47

Source: Pitt Street Research

Base and bull case differences

The only difference between our base and bull cases are the market penetration. We assume initially a 1% market penetration for the three AML indications and 0.3% market penetration for FTO cancers and cardioprotection. But from there, the growth accelerates faster. By FY32, our base case assumes a 22% penetration for the AML indications, but our bull case assumes 30%. For FTO cancers and cardioprotection, we assume that it can achieve an 8% share by FY32 in our base case and a 15% share in our bull case.

Risks to our investment thesis

We see the following major risks to RAC's investment thesis:

- **Clinical risk.** The clinical studies for Zantrene across different cancer indications could potentially produce outcomes that are unfavourable or below management's expectations, which would delay the commercialisation timelines for the product.
- **Regulatory risk.** There is a risk that approval in highly regulated markets such as the US and Europe takes longer-than-expected, resulting in a delay in attaining revenue generation status.
- **Execution/commercial risk.** Besides ensuring favourable clinical results, RAC will need to set up a strong marketing and logistics network to be able to sell Zantrene in global markets. The company will be unduly affected if it is unable to effectively execute its commercialisation plans.
- **Competition risk.** While RAC has a unique proposition to treat AML and other cancers, there are many small/medium-sized players developing different therapies for the treatment of AML, especially in the US. It will be imperative for the company to gain an early mover advantage in order to establish its presence in the market. We note, RAC has commercial exclusivity for 7 years post-commercialisation which should cover the life of our model.
- **Forex risk.** When commercialised, RAC's earnings will be in the local currency of applicable markets. Currency fluctuations can impact RAC's earnings in AUD. We used a 67.5 USD/AUD exchange rate but fluctuations impact our valuation. If we assume parity between the AUD/USD, our valuation drops to $4.48 base case and $7.31 bull case ceteris paribus. At the other extreme, if we assume US$1=A$2, our base case is $8.93 and our bull case is $14.55. Any M&A transaction involving Zantrene would be similarly impacted.

Comparable companies

For a comparable set of companies, we have looked at public companies listed on major US exchanges with a focus on developing therapies to treat AML. We further screened the list based on market capitalisation between US$50–600m (Figure 9). We have noted that that the company has no direct peer in the Australian listed market. Although RAC's potential is by no means limited to AML, we have restricted our search to AML companies for now because this will be the first indication Zantrene will be commercialised against.

Figure 9: Public comparable companies

Company	Location	Ticker	Market cap (US$m)	AML drug development phase	Website
ALX Oncology Holdings Inc.	US	NasdaqGS:ALXO	479.2	Phase Ib/II	www.alxoncology.com
Celularity Inc.	US	NasdaqCM:CELU	441.3	Phase I	www.celularity.com
Kronos Bio Inc.	US	NasdaqGS:KRON	299.7	Phase III	www.kronosbio.com
Vor Biopharma Inc.	US	NasdaqGS:VOR	185.7	Phase I/II	www.vorbio.com
Actinium Pharmaceuticals Inc.	US	NYSEAM:ATNM	130.1	Phase III	www.actiniumpharma.com
Magenta Therapeutics Inc.	US	NasdaqGM:MGTA	105.2	Phase I/II	www.magentatx.com
Curis Inc.	US	NasdaqGM:CRIS	94.6	Phase I/II	www.curis.com
GT Biopharma Inc.	US	NasdaqCM:GTBP	90.0	Phase I/II	www.gtbiopharma.com
Mustang Bio Inc.	US	NasdaqGM:MBIO	74.9	Phase I/II	www.mustangbio.com
MEI Pharma Inc.	US	NasdaqCM:MEIP	70.0	Phase Ib	www.meipharma.com
LAVA Therapeutics NV	Netherlands	NasdaqGS:LVTX	68.4	Phase I/IIa	www.lavatherapeutics.com
SELLAS Life Sciences Group Inc.	US	NasdaqCM:SLS	62.8	Phase III	www.sellaslifesciences.com
Syros Pharmaceuticals Inc.	US	NasdaqGS:SYRS	61.4	Phase II/III	www.syros.com
Race Oncology Ltd.	Australia	ASX:RAC	232.1	Phase II	www.raceoncology.com

Source: S&P Capital IQ, Pitt Street Research

ALX Oncology Holdings Inc. (NasdaqGS:ALXO) is a clinical-stage immuno-oncology company, focussing on developing cancer therapies. Its lead product candidate (ALX148) is a CD47 blocking therapy to be used for the treatment of myelodysplastic syndromes, AML, non-Hodgkin's lymphoma and solid tumours. It is currently in Phase Ib/II clinical trial.

Celularity Inc. (NasdaqCM:CELU) is a biotech company focussing on developing placental-derived allogeneic cell therapies for the treatment of cancer, immune and infectious diseases. It has five lead programmes including CYNK-001 which is a placental-derived unmodified natural killer cell. CYNK-001 is in Phase I clinical trial to treat AML and in Phase I/IIa trial for the treatment of glioblastoma multiforme and COVID-19.

Kronos Bio Inc. (NasdaqGS:KRON) is a biotech company focussing on dysregulated transcription factors to discover cancer drugs. The lead product candidate, entospletinib (ENTO), is an orally administered, selective spleen tyrosine kinase inhibitor for AML patients in Phase III clinical trial, currently in combination with induction chemotherapy.

Vor Biopharma (NasdaqGS:VOR) is a clinical-stage company focussing on developing engineered hematopoietic stem cell (eHSC) therapies for cancer patients. The lead eHSC product candidate, VOR33, is in Phase I/II to treat AML and other haematological malignancies. It has one other key drug in development to treat blood cancers.

Actinium Pharmaceuticals (NYSEAM:ATNM) focusses on developing and commercialising bone marrow transplant (BMT) and cellular/gene therapies for cancer treatment. Its lead product candidate, I-131 apamistamab (Iomab-B), is currently in Phase III clinical trial in patients over the age of 55 with active relapsed or refractory AML prior to receiving a BMT. It is also being studied with a CD19-targeted CAR T-cell therapy (Phase I).

Magenta Therapeutics Inc. (NasdaqGM:MGTA) develops treatments for blood cancers, genetic and autoimmune diseases using stem cell transplants. It has three drugs and a cell therapy programme including the lead candidate GTA-117 which targets HSCs and genetically mutated stem cells that cause AML and myelodysplastic syndromes. It is currently in Phase I/II clinical trial.

Curis Inc. (NasdaqGM:CRIS) is a biotech company engaged in developing cancer drugs. It has five drugs under development including emavusertib (an oral small molecule drug) which is currently in Phase I/II clinical trial for the treatment of non-Hodgkin lymphomas, AML and myelodysplastic syndromes.

GT Biopharma Inc. (NasdaqCM:GTBP) focusses on the development of immuno-oncology products. The lead drug, GTB-3550, is a single-chain tri-specific recombinant fusion protein conjugate. It is in Phase I/II clinical trial for the treatment of refractory/relapsed AML, myelodysplastic syndromes, advanced systemic mastocytosis and CD33+ malignancies.

Mustang Bio Inc. (NasdaqGM:MBIO) develops cell, CAR-T and gene therapies to potentially cure hematologic cancers, solid tumours and rare genetic diseases. Presently, it has nine programmes in different clinical stages including MB-102 CAR-T cell therapy in Phase I/II for the treatment of blastic plasmacytoid dendritic cell neoplasm, AML and myelodysplastic syndrome.

MEI Pharma Inc. (NasdaqCM:MEIP) is developing multiple drugs to treat cancer using three key investigational therapies – Zandelisib, Voruciclib and ME-344. Voruciclib is an oral cyclin-dependent kinase 9 inhibitor, which is in Phase Ib clinical trial for AML and B-cell malignancies.

LAVA Therapeutics NV (NasdaqGS:LVTX) is a Netherlands-based immuno-oncology company developing cancer treatments through its Gammabody platform. Its lead programme, LAVA-051, targets CD1d-expressing tumours and is currently in Phase I/IIa clinical trial for blood cancers including chronic lymphocytic leukaemia, multiple myeloma and AML.

SELLAS Life Sciences Group Inc. (NasdaqCM:SLS) is a biopharma company focussing on various cancer indications. The lead product candidate, galinpepimut-S (GPS), is a cancer immunotherapeutic agent that targets Wilms tumour 1. It is in Phase III clinical trials for the treatment of AML, and Phase I/II trials for the treatment for ovarian and other cancers.

Syros Pharmaceuticals Inc. (NasdaqGS:SYRS) is a biopharma company with three lead clinical drugs – Tamibarotene, SY-2101 and SY-5609. Tamibarotene is a selective retinoic acid receptor alpha (RARα) agonist, currently in Phase II/III trials for patients with AML and myelodysplastic syndrome. The other two drugs are in Phase I/II trials in patients with acute promyelocytic leukaemia (APL) and select advanced solid tumours.

Experienced leadership with skin in the game

RAC has a robust management team with extensive experience and skills in managing and growing healthcare businesses. We believe RAC's strong leadership possesses deep domain expertise to help the company implement its growth strategies. Moreover, the fact that key members of the leadership team currently own ~14% stake in the company should provide further confidence to investors in RAC's leadership.

The company's current leadership team includes:

Board of Directors

Dr. John Cullity, Non-Executive Chairman since April 2018, previously held senior executive roles with Sanofi-Aventis and Schering-Plough in the US, and has consulted to the World Health Organization and the World Bank. His experience includes providing strategic advisory services on mergers and acquisitions; partnering and financing to life science companies globally; and leading buy side transactions in oncology and diabetes. Besides his medical degree (MBBS) from the University of Western Australia and advanced training in haematology-oncology at QEII Medical Centre, Dr. Cullity has completed a Master of Science at the London School of Economics and an MBA at the Wharton School, University of Pennsylvania.

Mr. Phillip R Lynch is RAC's Managing Director and CEO since September 2020. Mr. Lynch has more than 30 years of experience working with J&J in the Asia-Pacific region. He has diverse experience across corporate development, strategy, financial performance, mergers and acquisitions, marketing and governance. Mr. Lynch is a business graduate from Monash University. He has completed his post-graduate studies from the University of Virginia Darden Business School and is a graduate from the Australian Institute of Company Directors (AICD).

Dr. Daniel Tillett was appointed as the Executive Director and Chief Scientific Officer in October 2019. Over the past 20 years, Dr. Tillett has had commercial experience in the biotechnology industry ranging from project management, sales and marketing, IP management, fundraising and start-up investing. He has a PhD from the University of New South Wales in Molecular Genetics and Biochemistry. Dr. Tillett has more than 40 scientific publications and granted patents in molecular biology, microbiology, genetics and biochemistry.

Ms. Mary Harney, Non-Executive Director since February 2021, is a specialist across sectors with about 20 years of Board and C-Suite executive experience. She has a host of expertise in various aspects of business management in innovation industries such as biotechnology, pharmaceuticals, health and agricultural spheres. Ms. Mary has undergraduate degrees in science and art history from Monash University and University of Melbourne, respectively, and international post-graduate qualifications in diagnostic cytopathology. She is also a Fellow of the Institute of Managers and Member of the AICD.

Management Team

Dr. David Fuller, Chief Medical Officer since April 2021, is an internationally experienced biopharmaceutical executive and physician. He has over 30 years of R&D experience covering large, mid and small capitalisation companies including pre-clinical and clinical development, medical and regulatory affairs and commercialisation. Dr. Fuller holds a Bachelor of Medicine/Bachelor of Surgery degree, and a Bachelor of Pharmacy, both from the University of Sydney. He is also a member of the American Society Clinical Oncology.

Professor Michael Kelso was appointed as RAC's **Principal Scientist** in May 2021. He is an internationally experienced researcher and has more than 25 years of R&D experience in medicinal chemistry including oncology, development of antimicrobial drugs and formulation of drugs. He has published 69 scientific research papers and 7 patents and has secured 18 grants from a number of institutions. Professor Kelso holds a Bachelor of Medicinal Chemistry from the University of Wollongong and a PhD from the University of Queensland.

Dr. Marinella Messina, Clinical Program Director since February 2020, is a highly experienced specialist in oncology clinical trials. Over the past 10 years, she has managed clinical trials across all development phases. She has worked with academic research investigators as well as bio pharmaceutical companies. Dr. Messina holds a Bachelor of Science from the Department of Microbiology at the University of Sydney and a PhD from the Faculty of Medicine at the University of Sydney.

Professor Borje S. Andersson was appointed as the **Chair of RAC's Clinical Advisory Board** in December 2019. He has received international acclaim in the field of leukaemia and stem cell transplantation while researching at MD Anderson Cancer Centre in Houston, Texas. He also invented IV Busulfan which is an FDA-approved drug used in stem cell transplantation. He received his medical degree from Karolinska Institute Faculty of Medicine and is board-certified in medical oncology, internal medicine and haematology.

Appendix I – Glossary

Anthracene – It is a crystalline aromatic hydrocarbon obtained by the distillation of crude oils and used in the manufacture of dyes and organic chemicals.

Anthracyclines – These are a class of drugs used in cancer chemotherapy that are extracted from streptomyces bacteria.

Cardiotoxicity – Heart damage that arises from certain cancer treatments or drugs which can develop years after cancer treatment, especially in adults.

Chemotherapeutic – These include drugs with the ability to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Deoxyribonucleic acid (DNA) – It is a molecule that comprises two chains that coil around each other to make a double helix. DNA carries genetic information, which is critical for the development, functioning, growth and reproduction of all identified organisms.

G-quadruplex – These are secondary DNA sequences formed from stacked guanine tetrads (group of fours). These are frequently used as an active area of genomic research.

Immunostimulatory properties – These are specific properties stimulated by substances (immunostimulators – drugs and nutrients) that increase the ability of the immune system to fight infection and disease.

Leukaemia – It is the cancer of body's blood-forming tissues, including the bone marrow and the lymphatic system.

Lymphoma – It is a cancer of the lymphatic system that begins in infection-fighting cells of the immune system, called lymphocytes.

Macrophages – These are a kind of white blood cells that surround and kill microorganisms, remove dead cells and stimulate the action of other immune system cells.

Melanoma – It is a tumour of melanin-forming cells, especially a malignant tumour associated with skin cancer.

Metastasis – It is the property of cancer cells to spread from the place where they first formed to another part of the body.

Multidrug resistance – It refers to the resistance of cancer cells to a broad variety of structurally and mechanistically different anticancer drugs.

Myeloma – It is a type of blood cancer that develops from cells in the bone marrow called plasma cells.

Precision oncology – It describes diverse strategies in cancer medicine that use information about a person's genes or proteins to prevent, diagnose or treat disease using personalised/targeted therapies.

Ribonucleic acid (RNA) – It is a biological macromolecule that converts the genetic information of DNA into proteins.

Research Governance Office (RGO) – It is an Australian organisation that provides an independent and systematic evaluation of research applications to minimise the risk and ensure the safety of the patient, the researcher and the institution.

Sarcoma – It is a type of cancer that begins in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue, or other connective or supportive tissue.

Appendix II – Capital structure

Class	In million	% of fully diluted	Note
Fully paid ordinary shares	159.4	92.0%	
Unlisted options	13.7	7.9%	Various options expiring during 2025-2027 with exercise price ranging from A$2.65 to A$4.90
Unlisted performance shares and rights	0.1	0.1%	
Fully diluted shares	**173.2**		

Source: Company

Appendix III – Major shareholders

RAC is predominantly owned by individual investors including insider members. The company's Chief Scientific Officer, Dr. Daniel Tillett, is the biggest shareholder with 8.5% of total shares outstanding. He is followed by Dr. John Cullity (Non-Executive Chairman) and William James Garner (former Non-Executive Director) who own 5.1% and 4.7% of the company's shares, respectively.

Appendix IV – Intellectual property

WO/2021/094827, *Use of bisantrene to treat measurable residual disease in acute myeloid leukaemia,* priority date 11 November 2011, invented by Dr. Daniel Tillett.

- The patent discloses a method to treat AML with a focus on eliminating the measurable residual disease and improve the outcome of hematopoietic stem cell transplantation by administering bisantrene (Zantrene) antineoplastic agent to the patient. It comprises intravenous delivery of a pharmaceutical composition containing bisantrene, bioavailability enhancers – such as mPEG-b-PLA (methoxy polyethylene glycol-b-poly (D-, L-lactide) micelles and beta-cyclodextrin – and additional therapeutic agents (e.g., arsenic trioxide, cytarabine and dexamethasone).
- Only a Patent Cooperation Treaty (PCT) application has been filed for the patent yet.

WO/2020/072948, *Method for preparing and delivering bisantrene formulations,* priority date 4 October 2018, invented by Daniel L. Levy and John Rothman.

- The patent discloses a method for preparing and intravenously delivering a pharmaceutical composition comprising bisantrene dihydrochloride and additional therapeutic agents (e.g., interleukins, telomerase inhibitors, methylation modulators and gamma secretase inhibitors). The formulation is delivered at a dosage of 200–300 mg/m^2 for a duration of 1.5–2.5 hours to reduce toxicity, improve bioavailability, and prevent venous damage and phlebitis. It is used to treat malignancies such as breast cancer, acute myelocytic leukaemia, myelodysplastic syndrome, chronic lymphocytic leukaemia and Hodgkin's lymphoma.

- Applications for the patent were filed in Australia, the US, Canada, China, South Korea and Europe, and has not been granted in any of these geographies yet.

WO/2019/073296, *Liposomal formulations of bisantrene or derivatives or analogs thereof,* priority date 13 October 2017, invented by John Rothman.

- The patent covers a pharmaceutical composition to treat malignant tumours that comprises bisantrene analogues/derivatives (such as bisantrene dihydrochloride) and additional therapeutic agents (e.g., cytarabine, fludarabine, all-trans-retinoic acid, interleukin-2 and arsenic trioxide) encapsulated by a liposome. The formulation offers reduced toxicity and improved bioavailability, and reduces the severity of circulatory system complications, e.g., phlebitis.
- Only a PCT application has been filed for the patent yet.

WO/2015/013581, *Combinatorial methods to improve the therapeutic benefit of bisantrene,* priority date 26 July 2013, invented by William Garner, Arnie Franklin and John Rothman.

- The patent discloses methods to improve the efficacy and reduce the side effects of a therapy involving administration of bisantrene for treating cancer – such as refractory breast cancer, AML and ovarian cancer. The methods include patient selection based on their metabolic enzyme levels, tolerance to GI toxicities, etc., and modifications in bisantrene-based drug composition/dosage (i.e., compositions containing additional drug compounds, e.g., thymidylate synthetase inhibitors and anti-tubulin agents) to maximise the therapeutic impact of the drug compounds.
- Applications for the patent were filed in Australia, the US, Canada, China, South Korea and Europe, and has been granted in the US.
- The US patent is expected to expire in 2034.

Appendix V – Papers

Valdez et. al. (2022), *Enhanced cytotoxicity of bisantrene when combined with venetoclax, panobinostat, decitabine and olaparib in acute myeloid leukaemia cells*, Leukaemia & Lymphoma, 63:7, 1634-164.

- The paper reviews a study to demonstrate the synergies attained with a combination of bisantrene and antineoplastic drugs – Venetoclax, Panobinostat, Decitabine and Olaparib – to treat AML. The combinatorial formulation offers enhanced cytotoxicity in AML cells and inhibits cell proliferation by enhancing DNA damage and potent apoptosis activation.

Canaani et. al. (2021), *A Phase II study of bisantrene in patients with relapsed/refractory Acute Myeloid Leukaemia*. Clinical Trial Eur J Haematol. 2021 Feb; 106(2):260-266. Epub 2020 November 2021.

- The paper reviews the response of patients with relapsed/refractory AML to a week-long intravenous infusion of bisantrene in a dosage of 250 mg/m^2 for 2 hours on each of the seven days. As per the study conducted on ten patients, the response rate was found to be 40%, with maximum effect in patients with EMD disease (e.g., breast chloroma and CNS). While the most frequently reported severe adverse events were

thrombocytopenia and mucositis, the administration of bisantrene did not cause recognisable cardiotoxicity.

Valdez et. al. (2021), *Synergism of the Anthracene-Derivative Anti-Cancer Agent Bisantrene with Nucleoside Analogs and A Bcl-2 Inhibitor in Acute Myeloid Leukaemia* Cells. J Clin Exp Oncol Vol: 10 Issue: 4, 25 March 2021.

– The paper pertains to a synergistic combination of bisantrene with nucleoside analogues – e.g., cytarabine, cladribine, fludarabine and clofarabine – and BCL-2 inhibitors (e.g., Venetoclax) to treat AML. The combinatorial formulation offers enhanced cytotoxicity in acute myeloid leukaemia cells and inhibits cell proliferation by enhancing DNA fragmentation and potent apoptosis activation.

Su et. al. (2020), *Targeting FTO suppresses cancer stem cell maintenance and immune evasion*. Cancer Cell. 2020 Jul 13; 38(1): 79–96.e11. Published online 11 June 2020.

– The paper pertains to two potent small-molecule inhibitors of FTO protein – bisantrene and brequinar – for cancer therapy in AML. Inhibition of the FTO protein – i.e., an RNA N6-methyladenosine (m^6A) demethylase – suppresses LSC/LIC (leukaemia stem/initiating cells) self-renewal, checkpoint gene expression and hypomethylating agent-induced immune evasion, helping treat leukaemia patients.

Appendix VI – Analysts' qualifications

Stuart Roberts, lead analyst on this report, has been covering the Life Sciences sector as an analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research specialty at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months in 2015 and 2016 doing Investor Relations for two ASX listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Science companies.
- In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Science companies.

Nick Sundich is an equities research analyst at Pitt Street Research.

- Nick obtained a Bachelor of Commerce/Bachelor of Arts from the University of Sydney in 2018. He has also completed the CFA Investment Foundations program.
- He joined Pitt Street Research in January 2022. Previously he worked for over three years as a financial journalist at Stockhead.
- While at university, he worked for a handful of corporate advisory firms.

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