MAY 2024

RACE ONCOLOGY

AT THE HEART OF CANCER CARE

INVESTOR PRESENTATION

ASX: RAC | RACE ONCOLOGY LIMITED | ABN 61 149 318 749

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Key highlights of Race Oncology

1. **Bisantrene** – derisked & clinically proven anticancer drug offering ~80%[1] chance of success - not the 3% common in oncology
2. Solves a real & significant health problem – heart damage caused by chemotherapy, a rising issue due to an ageing population and greater post-cancer longevity
3. Bisantrene builds on a major existing market of 20m anthracycline doses/year potential sales >US$5B/year
4. Low-cost development with an opportunity for a rapid pathway to market via the FDA accelerated approval process from Phase 2
5. Management invested with proven technical, deal & ASX track record

1. MST Access Report: New RC220 formulation achieves significant milestone, 02 May 2024

Corporate snapshot

Race Oncology is an ASX-listed, clinical stage biopharmaceutical company with a dedicated mission to be at the heart of cancer care.

Key data

ASX code	RAC
Share price	$1.41[1]
Market capitalisation	$234.6m[1]
Cash at bank	$16.2m[2]
Debt	Nil
Enterprise value	$218.4m[1]
Shares on issue	166,385,129[1]
Options on issue	29,169,753[1]

1. *As at 10 May 2024*
2. *As at 31 March 2024*

Race 12-month trading history

Current Bonus & Piggyback Options Offer

On 22 November 2023, Race issued a 1 for 20 bonus and piggyback option series to existing shareholders to raise up to $36.6 million to fund future clinical activities in anticancer + cardioprotection, m^{6}A RNA and AML.

Race board and management team

BOARD OF DIRECTORS

Mary Harney
Non-Executive Board Chair

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PeterMac Peter MacCallum Cancer Centre Victoria Australia
Oncology One

Dr Peter Smith
Executive Director

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LA TROBE UNIVERSITY

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Bristol Myers Squibb
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Forbes AUSTRALIA
BREAST CANCER TRIALS

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Principal Scientist

Scripps Research

Dr Marinella Messina, PhD
Clinical Director

NOXOPHARM
Datapharm Australia
KOLLING Institute of Medical Research

Bisantrene's history of clinical success

Breast cancer[1]

471 patients across 9 Phase 2 & 3 clinical trials

Less toxic than standard-of-care doxorubicin
- lower myelosuppression
- lower alopecia (hair loss)
- no cardiac failures

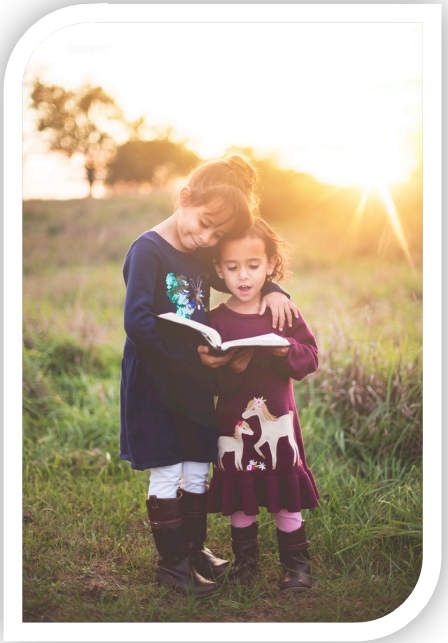
Phase 3. Overall patient survival greater in bisantrene treated patients (HR 0.92 95%CI = 0.7-1.21)

Acute Myeloid Leukaemia

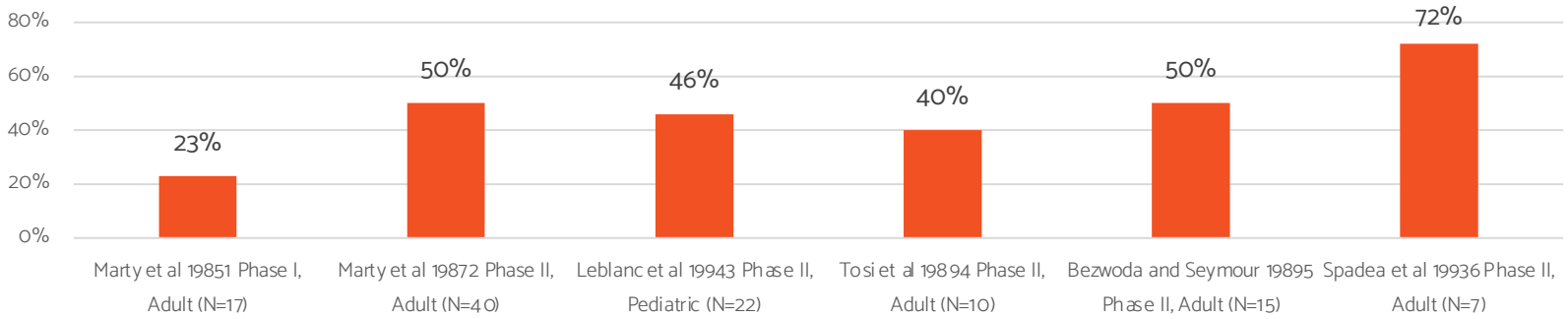
Approved in France in 1988, but Lederle ended commercial development of bisantrene due to solubility issues

Complete response rates above 40% as a salvage agent for Acute Myeloid Leukaemia (AML)

Bisantrene cured two French girls with r/rAML in the 1980 & 90s. Both women are alive today and have their own families

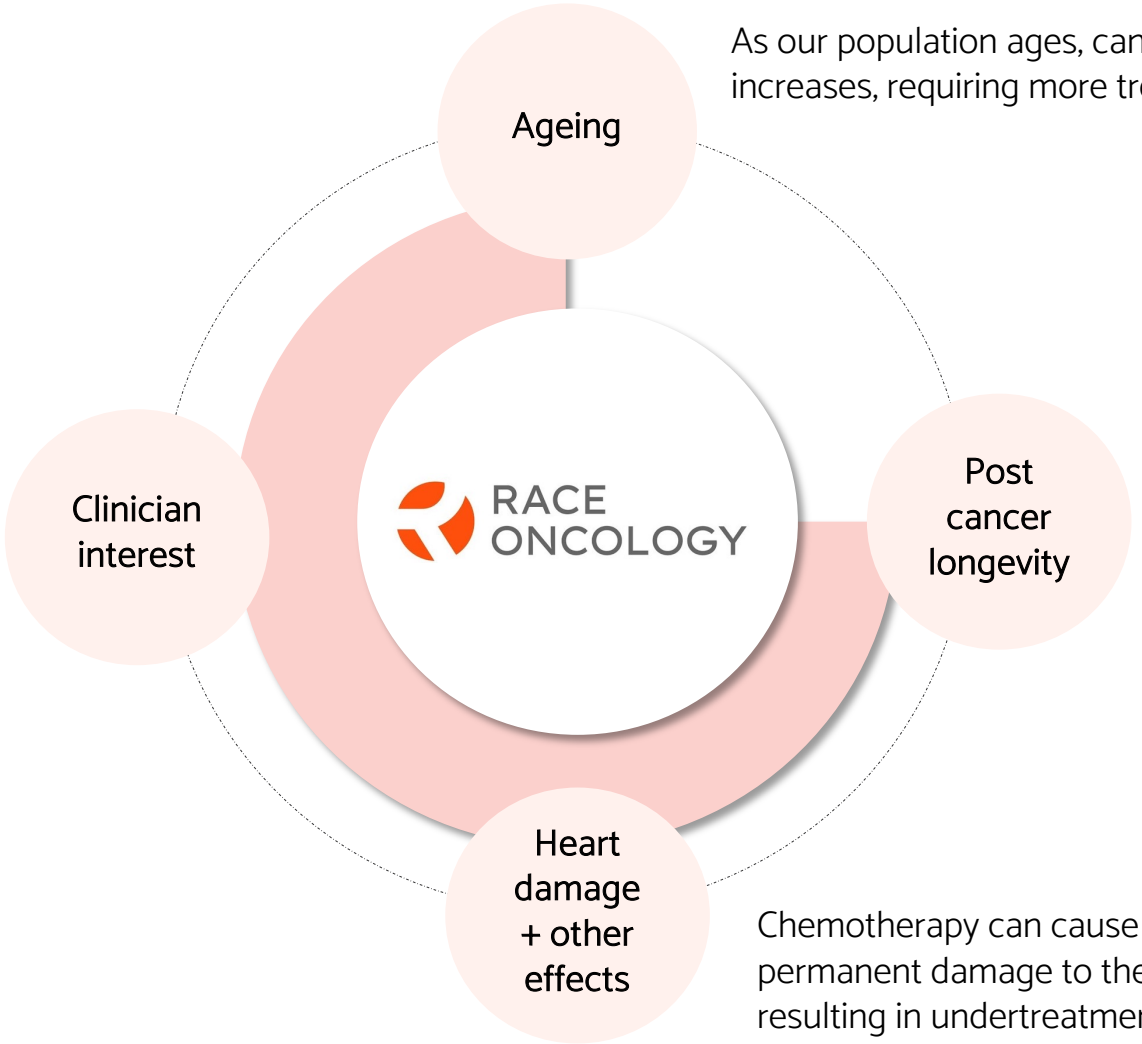


Complete responses with bisantrene in paediatric and adult Acute Myeloid Leukaemia patients



1. Cowan, J. D. et al. . Natl. Cancer Inst. 83, 1077–1084 (1991).

Major themes in cancer chemotherapy



As our population ages, cancer diagnosis increases, requiring more treatments

Growing clinician understanding of chemotherapy cardiotoxicity is driving strong interest in better treatment options

Improved cancer treatment leads to patients living longer with serious post-treatment side effects

Chemotherapy can cause serious & permanent damage to the patient's heart resulting in undertreatment

Chemotherapy needs improvement

Anthracyclines are the most widely used class of chemotherapeutics. They are highly effective, but can **cause permanent damage** to the hearts of patients

Current solution – **exclude use** in high-risk patients and **reduce dosing** of the drugs

Issue – patients not given full effective dose level & heart damage with long-term serious health consequences remains

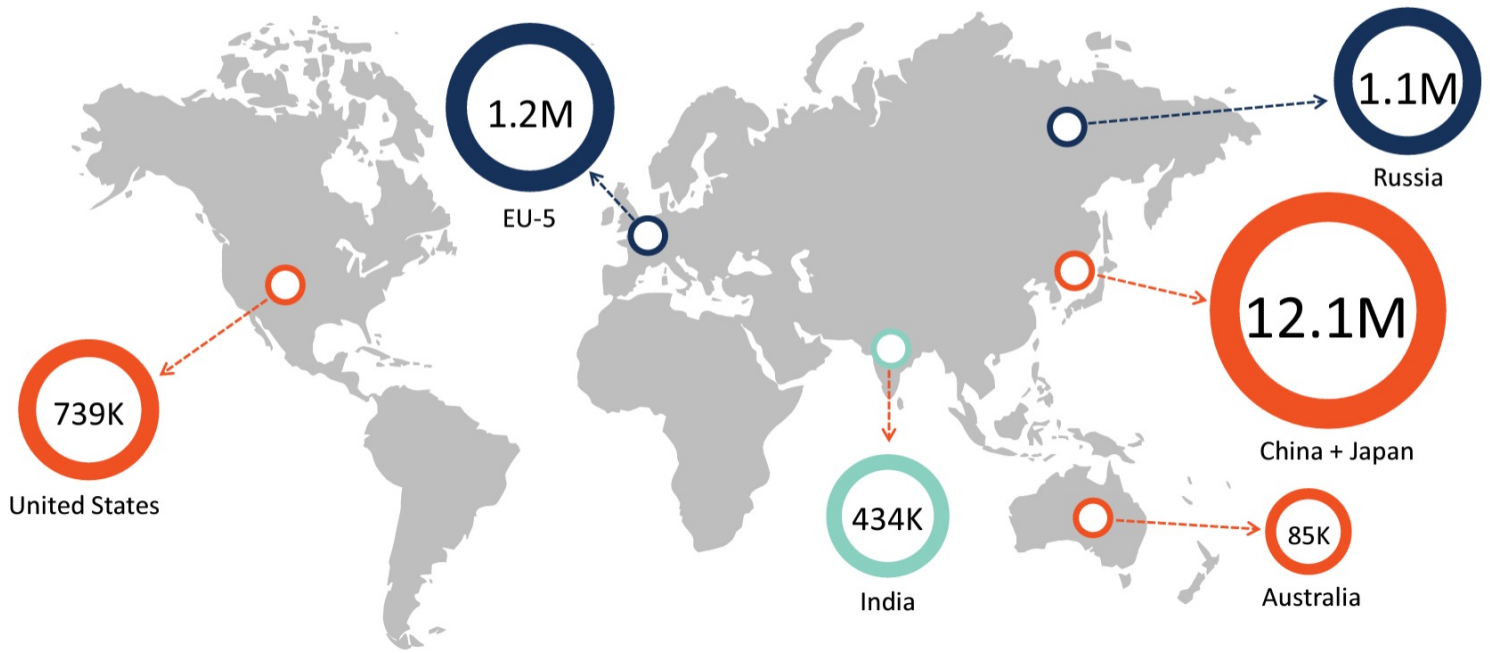
Opportunity – if the cardiotoxicity could be reduced, it would allow for **more patients to be treated and receive a more effective therapeutic dose**

"Cardiotoxicity, which includes heart failure, is one of the main side effects limiting the use of these effective therapies."

Professor Aaron Sverdlov, University of Newcastle

Global anthracycline chemotherapy use[1]

Global anthracycline usage[1]



FDA approved uses[2,3]

Acute lymphocytic leukemia	Ewing sarcoma
Acute nonlymphocytic leukemia	Soft tissue sarcoma
Acute myelogenous leukemia	Bone sarcoma
Hodgkin's lymphoma	Thyroid sarcoma
Non-Hodgkin's lymphoma	Neuroblastoma
Bladder cancer	Wilms tumor
Breast cancer	Small cell lung cancer
Ovarian cancer	Gastric carcinoma
Osteogenic sarcoma	Bronchogenic carcinoma
AIDS-related Kaposi's sarcoma	Prostate cancer
	Multiple myeloma

Other uses[2,3]

Advanced Endometrial Cancer
Uterine Sarcoma
Metastatic Hepatocellular Cancer
Advanced Renal Cell Carcinoma
Thymomas & Thymic Malignancies
Waldenstrom Macroglobulinemia

1. Estimated number of anthracycline doses used per year – Triangle Insights (ASX Announcement: 14 April 2023)
2. Daunorubicin, doxorubicin, liposomal doxorubicin (Doxil), epirubicin, idarubicin, mitoxantrone, and valrubicin
3. Triangle Insights (ASX Announcement: 14 April 2023)

Building on bisantrene's history

Race has...

- Taken the clinically validated oncology drug bisantrene and fixed the formulation issues that caused it to be discontinued[1]
- Created valuable new intellectual property with a long lifespan (20 years)
- **Leveraged new science to discover how bisantrene works and find the indications with greatest value (cardioprotection + anticancer)**[2]
- Built on the >1,500 patients worth of existing clinical data across a deep and broad range of cancer indications to inform findings and generated **new Phase 2 clinical data in AML**
- Undertaken primary market research to quantitate the **multi-billion dollar market opportunity offered by bisantrene** and identify where the drug fits into the patient treatment paradigm[3]

RC220 is a clinically and commercially attractive formulation with long IP life

1. ASX Announcement: 9 November 2023 | 2. ASX Announcement: 21 September 2023 | 3. ASX Announcement: 21 September 202 April 2023

New bisantrene formulation - RC220[1]

RC220 – a high value drug reformulation

- In the 1980s, Lederle (now Pfizer) tried and failed to solve issues around the poor solubility of bisantrene which necessitated its delivery via an invasive central line catheter
- Race's proprietary formulation, RC220 enables peripheral intravenous administration (IV), which dramatically expands the potential patient population and market
- RC220 preserves the activity and PK/PD properties of the prior clinically validated bisantrene formulation
- **Provides strong IP protection** – expected patent life into 2044
- Considered a new drug product by regulators and so requires a new non-clinical toxicology & safety data package – expected Q2 2024
- cGMP drug product completed on-time in Q1 2024 by Ardena

RC220 is expected to be available for clinical use H2 2024[1]

1. ASX Announcement: 9 November 2023

Bisantrene + doxorubicin Improved anticancer activity[1]

Bisantrene shows potent cell-killing activity against a diverse range of human cancers when used alone and in combination with doxorubicin, the most commonly used anthracycline

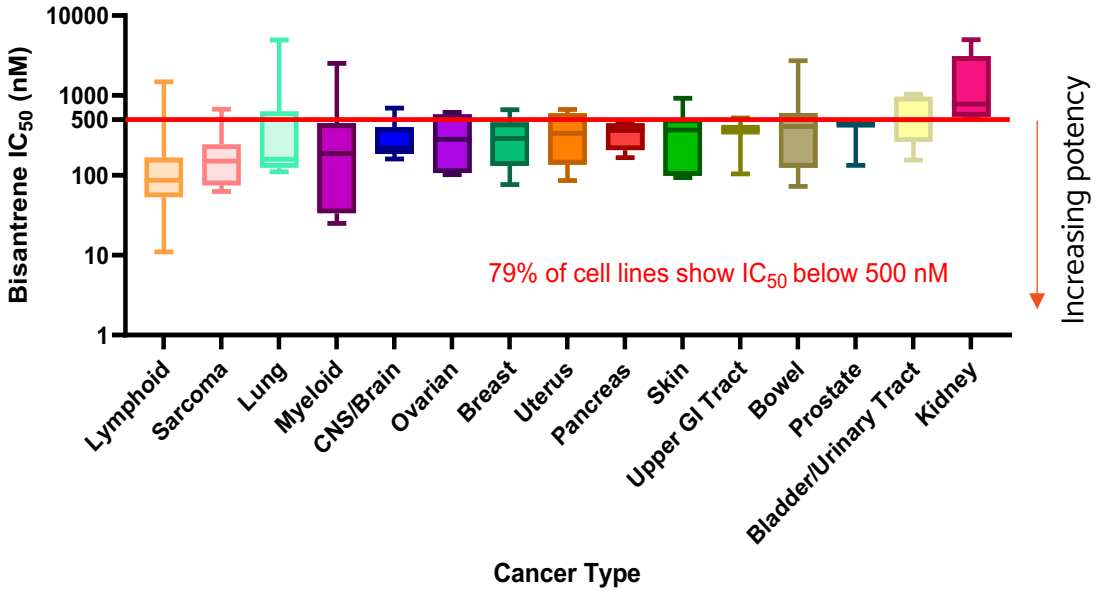


Figure 1. Bisantrene shows broad anti-cancer activity. The half-maximal inhibitory concentration (IC_{50}) was determined for bisantrene against 143 cancer cell lines derived from diverse human tumour types. Boxes show the 25%-75% range, with the line within each box representing the median IC_{50} value. The upper and lower edges of the box represent the 75th and 25th percentiles, respectively. Whiskers show the minimum and maximum IC_{50} values observed for each cancer cell type.

Bisantrene improves doxorubicin cell killing activity in

85% of all cancers[2]

1. ASX Announcement: 21 September 2023 | 2. 143 cancer cell lines screened.

Bisantrene + doxorubicin Protecting the heart[1]

Bisantrene protects the hearts of mice from permanent damage caused by the anthracycline doxorubicin.

Heart protection was achieved using higher levels of chemotherapy treatment with no extra toxicity observed.

Data supports using bisantrene with anthracyclines to protect the hearts of patients from chemotherapy.

Promise of better cancer treatment with less side effects.

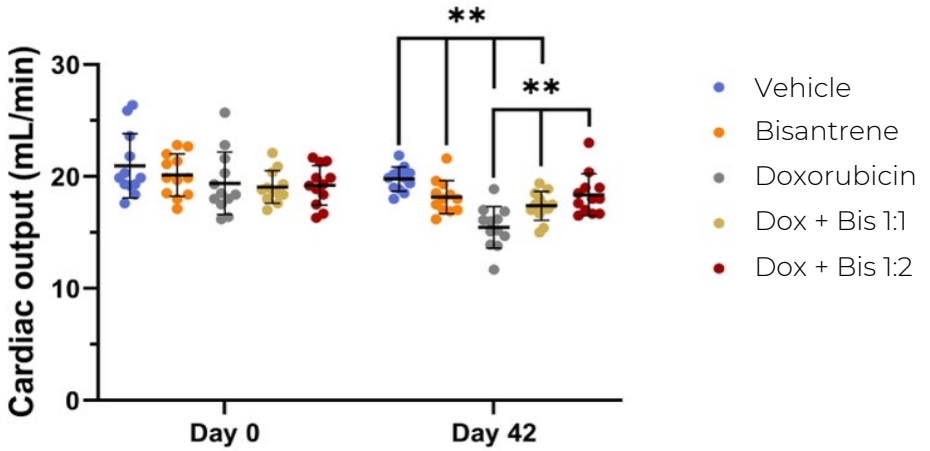
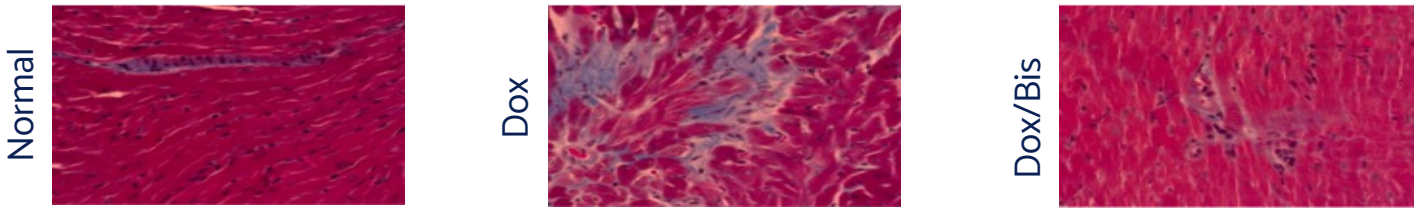


Figure 1. Cardiac output of C57BL/6 mice treated with either vehicle control (blue), bisantrene alone (orange), doxorubicin alone (grey), 1:1 molar ratio doxorubicin + bisantrene (yellow), or 1:2 molar ratio doxorubicin + bisantrene (red) at Day 0 and Day 42. All mice were dosed intravenously weekly with either: vehicle control, 7.33 mg/kg bisantrene, 5 mg/kg of doxorubicin, 5 mg/kg of doxorubicin + 3.67 mg/kg of bisantrene, 5 mg/kg of doxorubicin + 7.33 mg/kg of bisantrene. n=12 per group. Error bars = SEM. **p < 0.01.

Strong protection from anthracycline-induced cardiomyopathy



No Fibrosis | Extensive Fibrosis | Minimal Fibrosis

In vitro studies in human primary cardiomyocytes and in vivo studies in mice have demonstrated cardioprotection for the bisantrene + doxorubicin combinations, including increased cardiac function and reduced fibrosis when compared to doxorubicin alone

1. ASX Announcement: 30 June 2022

Views of key opinion leaders

> Scope for new cardioprotective therapy in addition to doxorubicin if it increases anticancer efficacy

Dr Chau Dang
Medical Oncologist (Breast Cancer)
Memorial Sloan Kettering Cancer Center
NY, USA

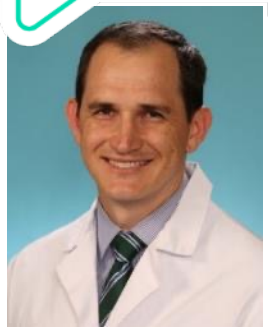
> 9-14% of patients on anthracycline regimens develop symptomatic cardiac dysfunction

Prof Aaron Sverdlov
Cardiologist
University of Newcastle, NSW, Australia

> It depends how carefully you look, but at least 30% of patients who are treated with anthracyclines have evidence of cardiac toxicity

Prof Tom Neilan
Cardio-Oncologist
Harvard Medical School, Boston, MA, USA

> Toxicity is highest in the first year, but risk of heart failure remains increased for the rest of their life



Prof Josh Mitchell
Cardio-Oncologist
Washington University, St Louis, MO, USA

> I am passionate about reducing the burden of cardiovascular disease for cancer patients

A/Prof Erin Howden
Head of the Cardiometabolic Health and Exercise Physiology Lab and Co-Lead of the Physical Activity program at the Baker Heart and Diabetes Institute, Melbourne, Australia

Memorial Sloan Kettering Cancer Center

THE UNIVERSITY OF NEWCASTLE AUSTRALIA
CARDIO-ONCOLOGY NEWCASTLE

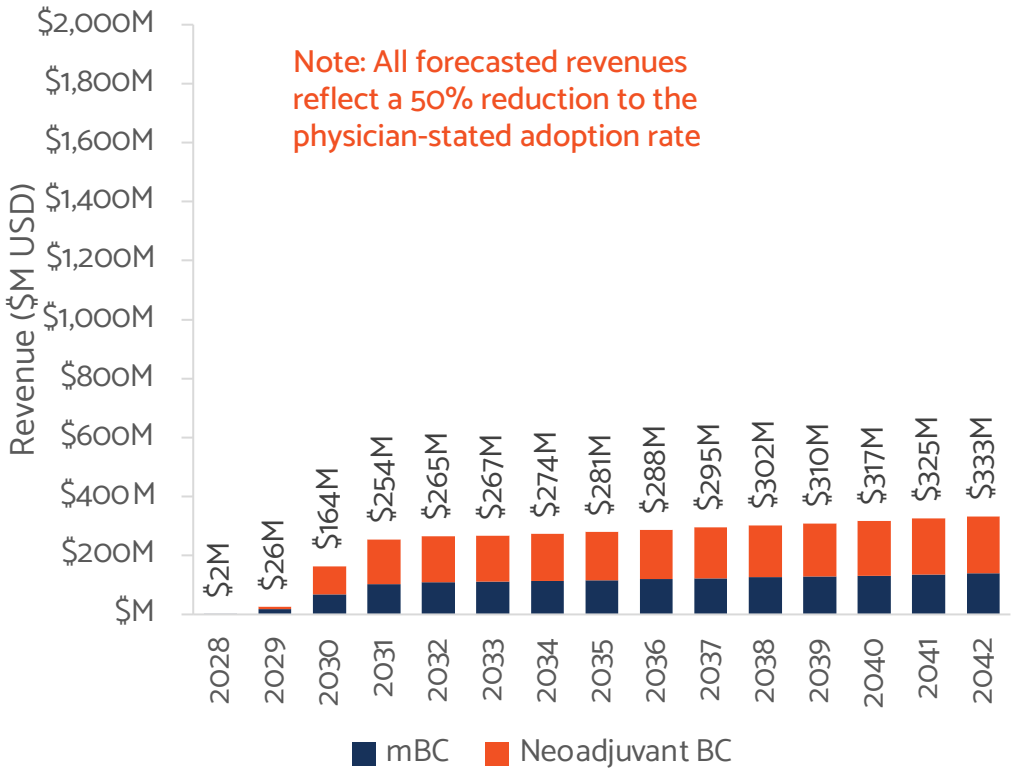
HARVARD MEDICAL SCHOOL

Washington University in St. Louis

Baker HEART & DIABETES INSTITUTE

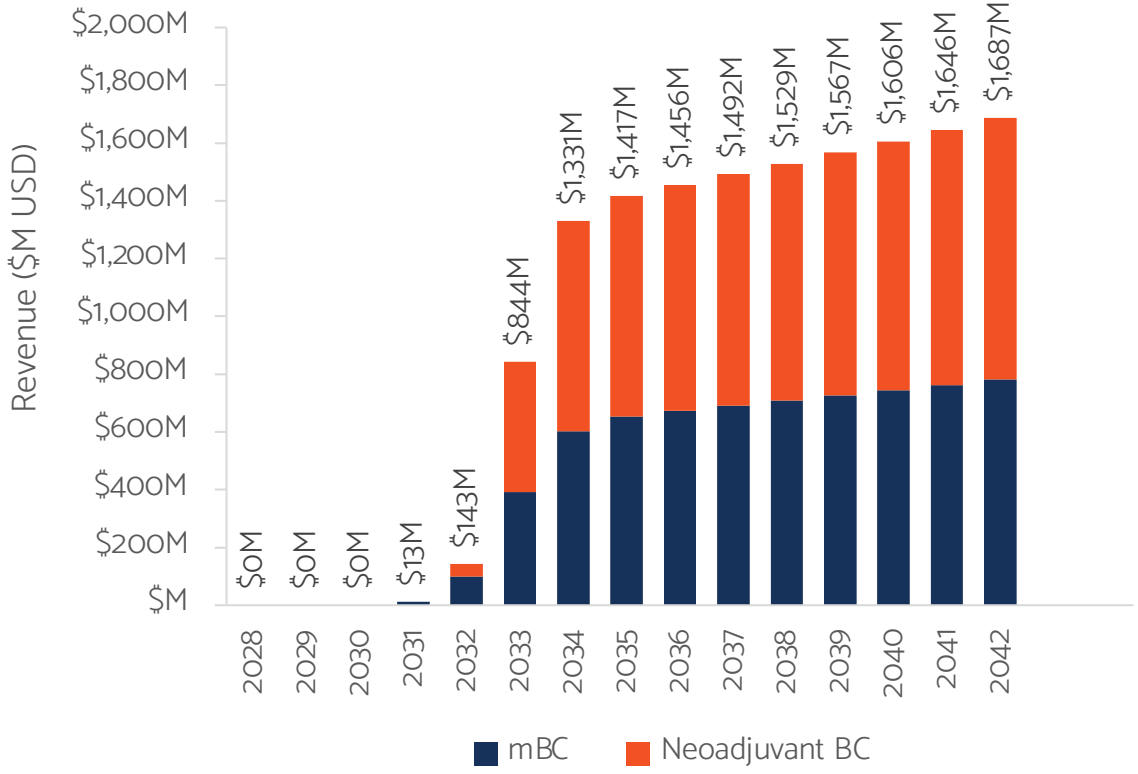
Bisantrene Market Potential – USA[1]

Annual Revenue – Cardioprotection alone in breast cancer indications



USD$4,000 base price/cycle for 4 cycles with a 3% annual net price increase after launch

Annual Revenue - Cardioprotection + anticancer activity in breast cancer indications

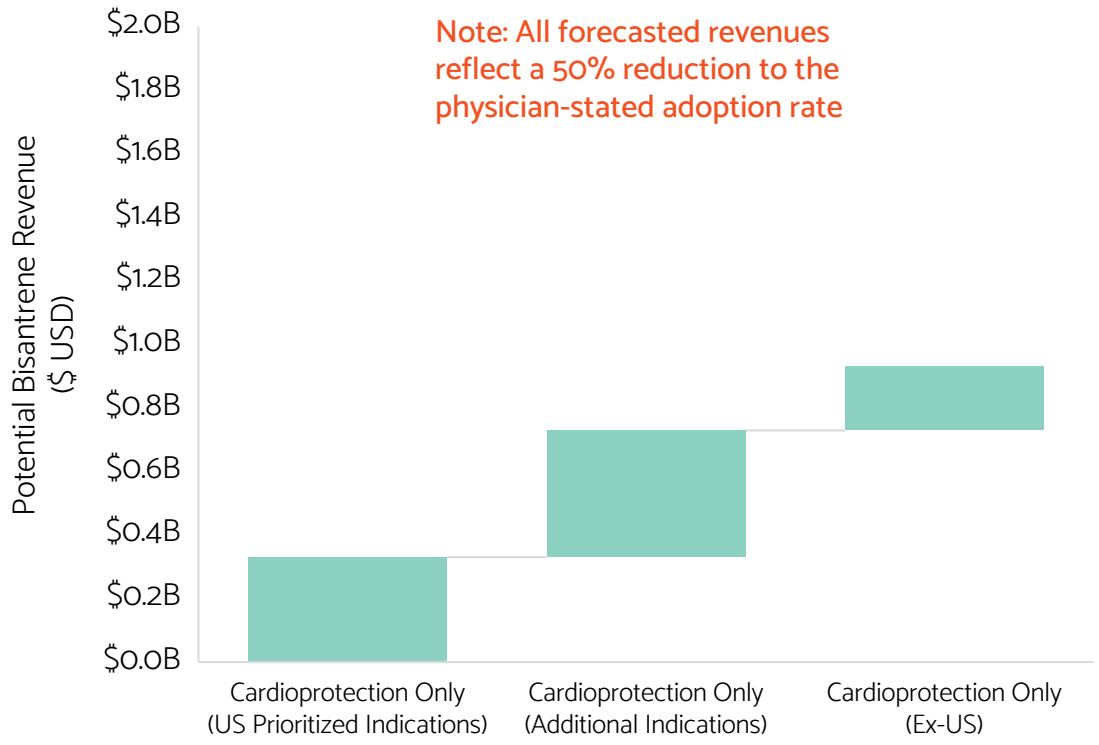


USD$15,000 base price/cycle for 4 cycles with a 3% yearly net price increase after launch

mBC = metastatic breast cancer; BC = breast cancer | 1. Triangle Insights (ASX Announcement: 14 April 2023)

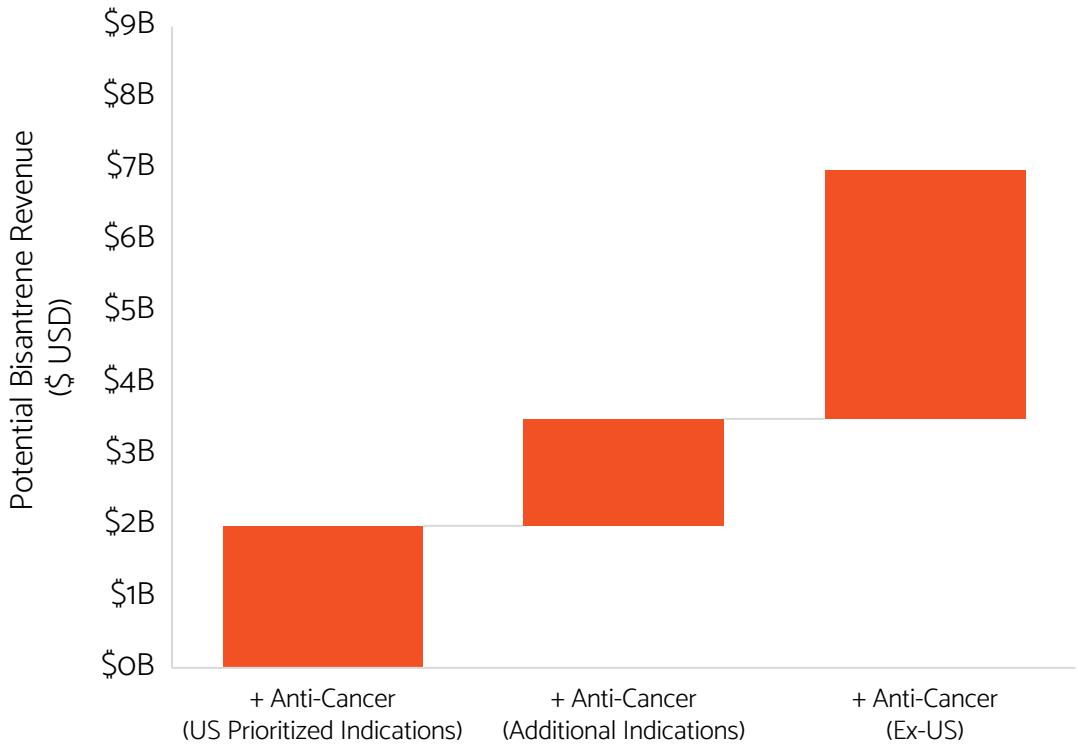
Bisantrene Market Potential – World[1]

Annual Revenue – Cardioprotection Only



USD$4,000 base price/cycle for 4 cycles with a 3% annual net price increase after launch

Annual Revenue - Cardioprotection + Anticancer



USD$15,000 base price/cycle for 4 cycles with a 3% yearly net price increase after launch

1. Triangle Insights (ASX Announcement: 14 April 2023)

Clinical pipeline

Asset	Indication	Sponsor	Discovery	IND enabling	Phase 1	Phase 2	Phase 3	Next milestone
RC110	Acute Myeloid Leukaemia	Chaim Sheba Medical Centre, Israel	Phase 2					In final stages of trial
RC220	Cardioprotection + m6A RNA + anticancer efficacy - solid tumours	Race Oncology	Phase 1a/b		H2 CY24	2026		Ethics / governance approvals First patient dosed
RC220	Acute Myeloid Leukaemia	Investigator sponsored[3]	Phase 1/2		H2 CY24			Confirmation of trial
m^6A RNA molecule development	Next generation bisantrene	Race Oncology	Preclinical					Preliminary results

RC220 cardioprotection clinical program

An 'all comers' Bayesian dose escalation Phase 1a trial of RC220 in any solid tumour patient where anthracycline use is indicated

Size: 25-50 patients; up to 10 sites in Australia and internationally
Sponsor: Race Oncology
Primary endpoints: Safety & optimal Phase 2 dose
Exploratory endpoints: Standard & advanced cardiac markers including VO_2Peak, m^6A RNA levels, & anticancer efficacy
Start: First patient H2 CY2024 (subject to RC220 availability)
Timeline: 12–18 months due to Bayesian design uncertainty around total patient number (patient recruitment)

Cohort extension (Phase 1b) in patient sub-groups to optimise bisantrene dosage in different drug combination settings

Expands market potential of bisantrene beyond breast cancer to all cancers where anthracyclines are used

Effect of bisantrene on the m^6A RNA system will be collected by using a lead-in dose of bisantrene given 7 days prior to the first anthracycline combination dose – provides 'clean' PK/PD, m^6A RNA & single-agent anticancer efficacy data

Cost: A$11 million, fully funded (based on 50 patients)

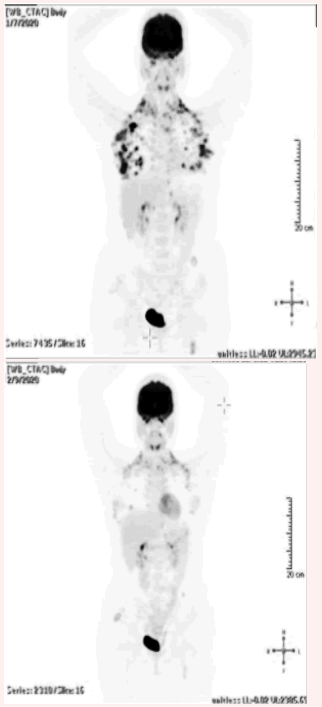
VO_2Peak offers a clinically relevant endpoint that can provide clear evidence of cardioprotection and improvement in patient Quality of Life

AML clinical program

Bisantrene was approved for AML in France in 1988, but never marketed. Two recent studies provide current day evidence that bisantrene is safe and efficacious

- **Sheba 1 (2020)** – 40% response rate in 10 AML salvage patients using bisantrene as a single agent – 4/4 clinical response in EMD AML[1]
- **Sheba 2 (2023)** – 40% response rate in 15 heavily pre-treated AML salvage patients with combination treatment[2]

The new data has sparked increased clinician interest in bisantrene



AML Phase 1/2 investigator initiated trial[3, 4]

A low intensity salvage treatment for patients unable or unwilling to tolerate high intensity chemotherapy who have failed standard of care AML treatments

Size	40-60 patients; up to 10 sites in Australia
Sponsor	Investigator
Primary endpoints	Safety & tolerability of bisantrene; Overall Response Rate
Exploratory endpoints	Event-free Survival; Overall Survival; Time to remission; Frailty scores; Time on treatment; Molecular response; Cardiac markers; Quality of Life
Start	Late H2 2024/early H1 2025
Timeline	18-24 months recruitment + 2 year follow up; interim results in 24 months

Trial to use low dose bisantrene (RC220) in combination with oral decitabine (ASTX727) (Astex)

Will provide clinical efficacy data supporting the use of bisantrene in low intensity AML combination protocols that are compatible with standard of care use of venetoclax

1. ASX Announcement: 16 June 2020 | 2. ASX Announcement 6 November 2023 | 3. Proposal as received from the Investigator in November 2023. May be subject to modification | 4. Fully funded from 75% or greater bonus option conversion in June 2024

Recent & coming milestones[1]

H2 CY2023 / H1 CY2024	H2 CY2024	H1 CY2025
✓ Interim results released from Sheba 2 study of bisantrene RC110 in AML patients – 40% response rate	Ethics submission for Phase 1a/1b trial in solid tumours	Additional preclinical results on bisantrene mechanism of action
✓ Proposal received for investigator led study of RC220 in AML patients	Governance approval for Phase 1a/1b trial in solid tumours	File Investigational New Drug (IND) application with US Food and Drug Administration for RC220
✓ cGMP RC220 manufacturing campaign completes	First patient treated in the RC220 solid tumour (all comers) Phase 1a/b Trial	First patient treated in Phase 1/2 AML study
✓ Leading cardiorespiratory expert, A/Prof Erin Bowden joins SAB	Updates on new molecules to target the m^{6}A RNA pathway	Initial results for RC220 solid tumour trial
✓ cGMP RC220 released by Ardena for use in human clinical trials	Publication of results from Sheba Phase 2 clinical study in AML	
✓ Bisantrene shows potent anti-cancer activity in AML models	Updates on clinical trial progress for RC220 cardioprotection study	
Completion of RC220 non-clinical safety and toxicology studies	Commence Phase 1/2 AML study	

1. All dates are estimates and subject to change

Key highlights of Race Oncology

1. **Bisantrene** – derisked & clinically proven anticancer drug offering ~80% chance of success - not the 3% common in oncology
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3. Bisantrene builds on a major existing market of 20m anthracycline doses/year potential sales >US$5B/year
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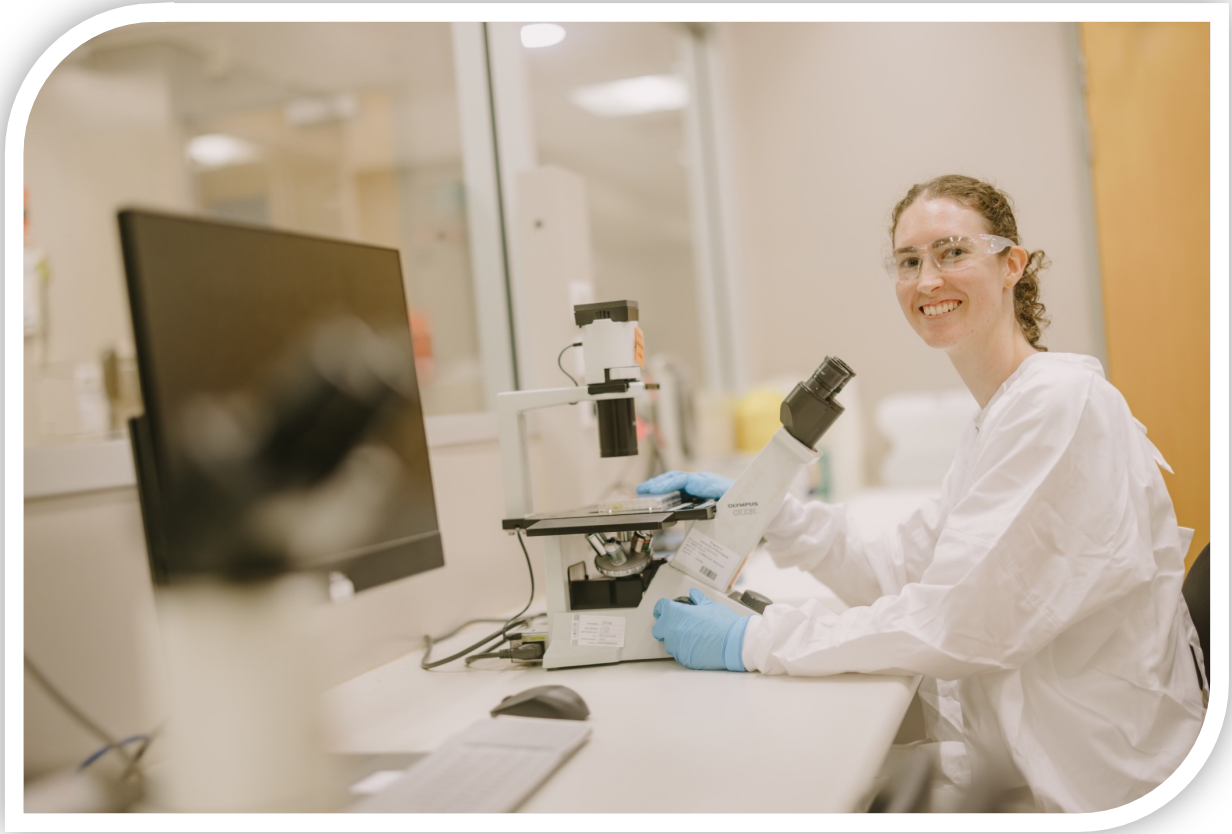

Questions

Race Oncology

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Authorised for release by CEO

RACE ONCOLOGY

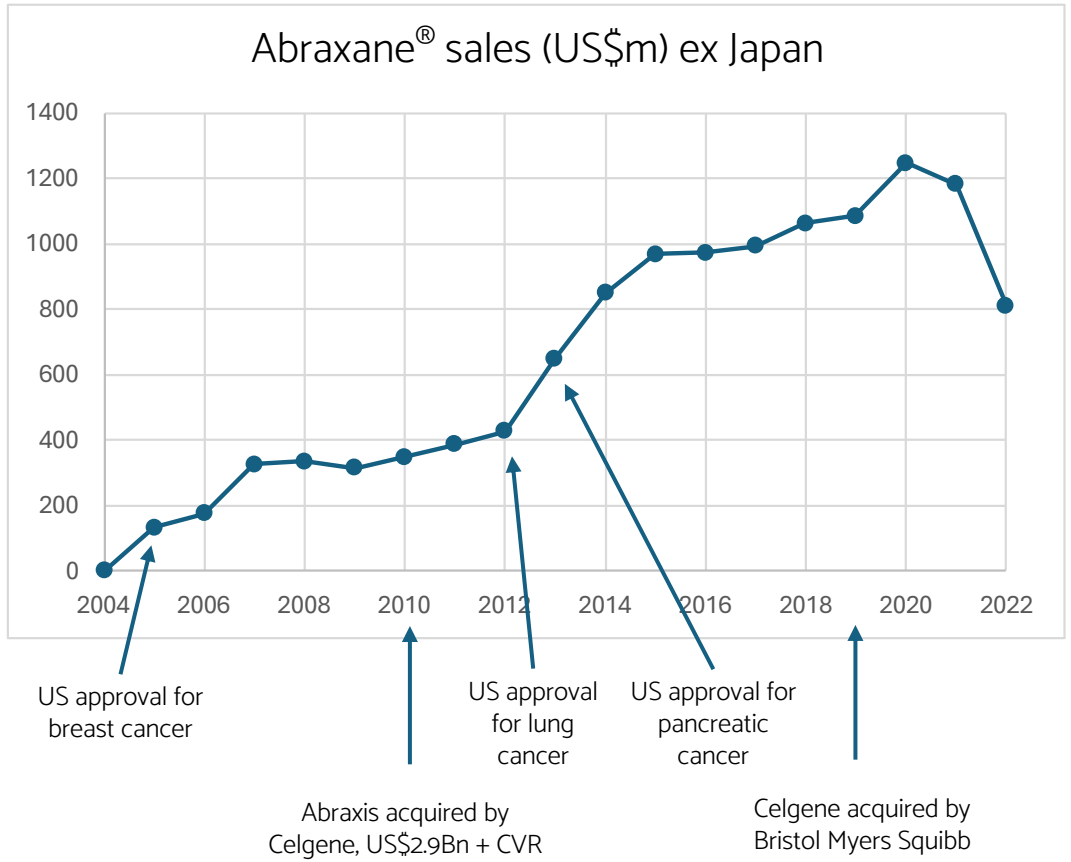
Appendix

Reformulations can build immense value

Abraxane (nab-paclitaxel) case study

- BMS developed the branded drug, Taxol® which was approved for Ovarian Cancer (1992), Breast Cancer (1994) and Non-Small Cell Lung Cancer (1999)
  - Taxol is formulated in Cremophor EL, requiring long infusions and steroid pre-treatment to reduce hypersensitivity reactions[1]
  - By 2000, sales of Taxol exceeded US$1.5 Bn
- A nanoparticle formulation of paclitaxel was developed by American Biosciences Inc to overcome the solubility issues. It was ultimately marketed by Abraxis Oncology using the brand name Abraxane®
- Abraxane established itself as the preferred taxane[2] at a branded drug price because it offered:
  - Shorter infusion time (30mins vs 3hrs)
  - No hypersensitivity/infusion reactions and no need for steroid pre-treatment
  - In some trials, Abraxane demonstrated clinical superiority over Taxol

Drug sales and company acquisition[3]

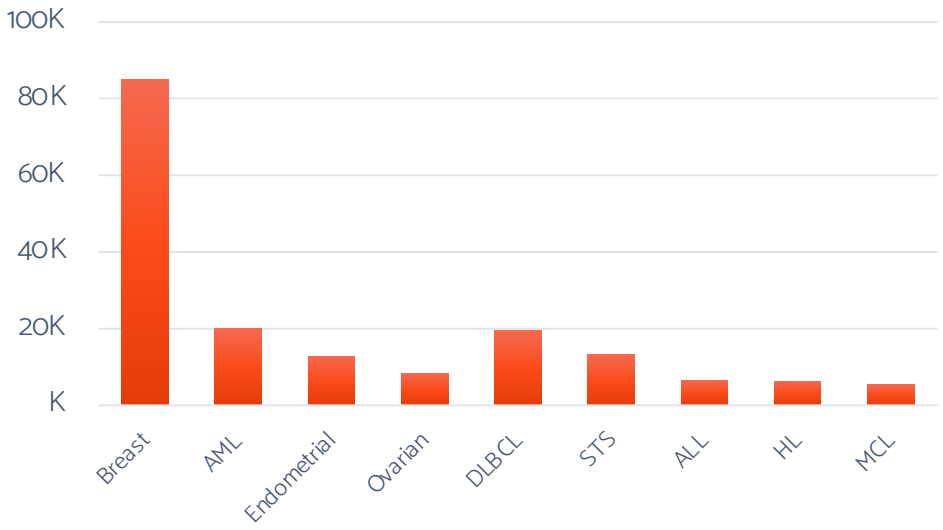


1. Gallego-Jara et al., 2020 | 2. Lee et al., 2020

3. www.sec.gov company filings and press releases from ABI, CELG and BMS

Anthracyclines in the USA[1]

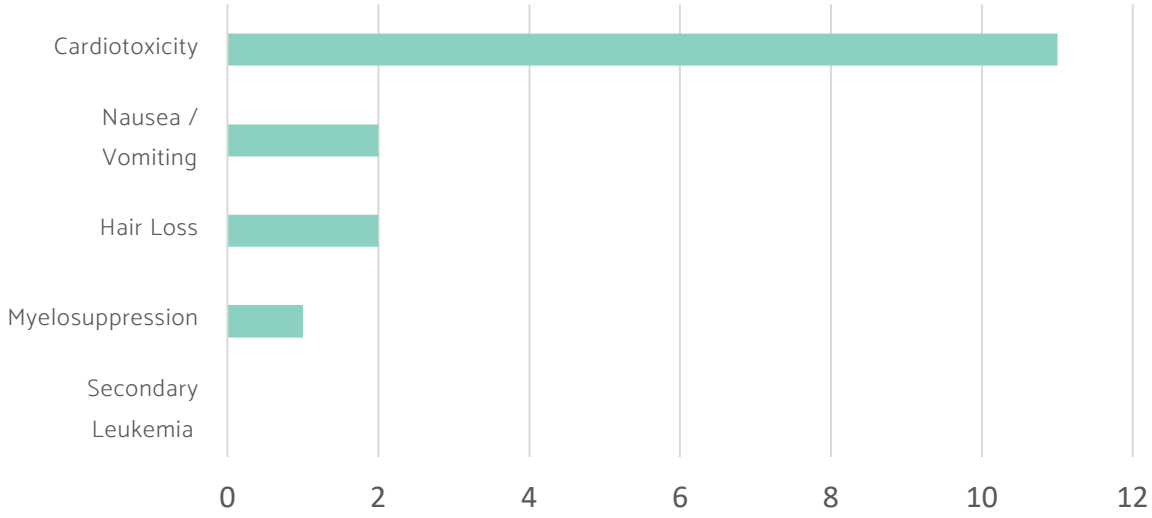
Anthracyclines continue to be widely used in the USA despite cardiotoxicity risks[2]



AML = acute myeloid leukaemia; DLBCL = diffuse large B cell lymphoma; STS = soft tissue sarcoma; ALL = acute lymphoblastic leukaemia; HL = Hodgkin's lymphoma; MCL = mantle cell lymphoma

There is strong US clinician interest in new agents able to reduce anthracycline cardiotoxicity[3]

Q. On a scale from 1 to 7, with one being 'not at all concerning' and 7 being 'extremely concerning', how concerning are the following anthracycline adverse events?

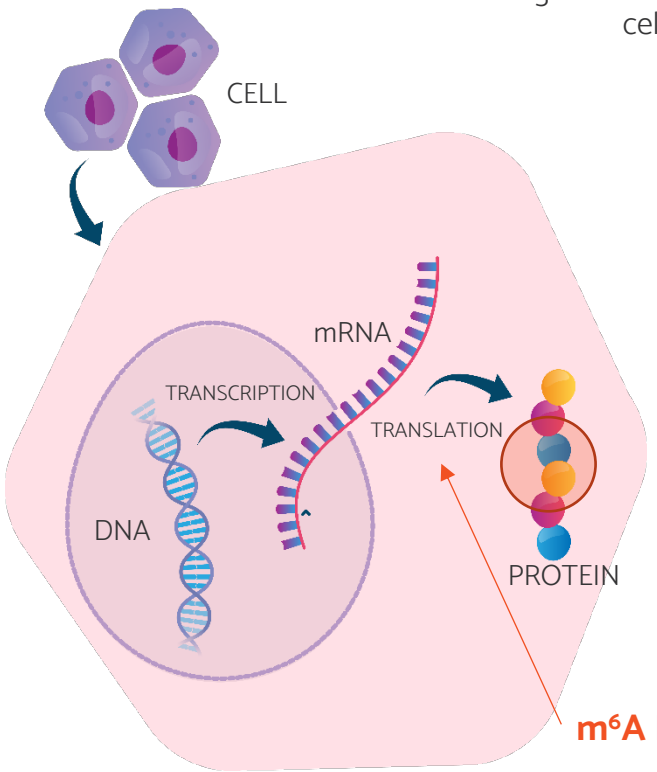


Count of times each US clinicians ranked a side effect as most concerning (n=16)

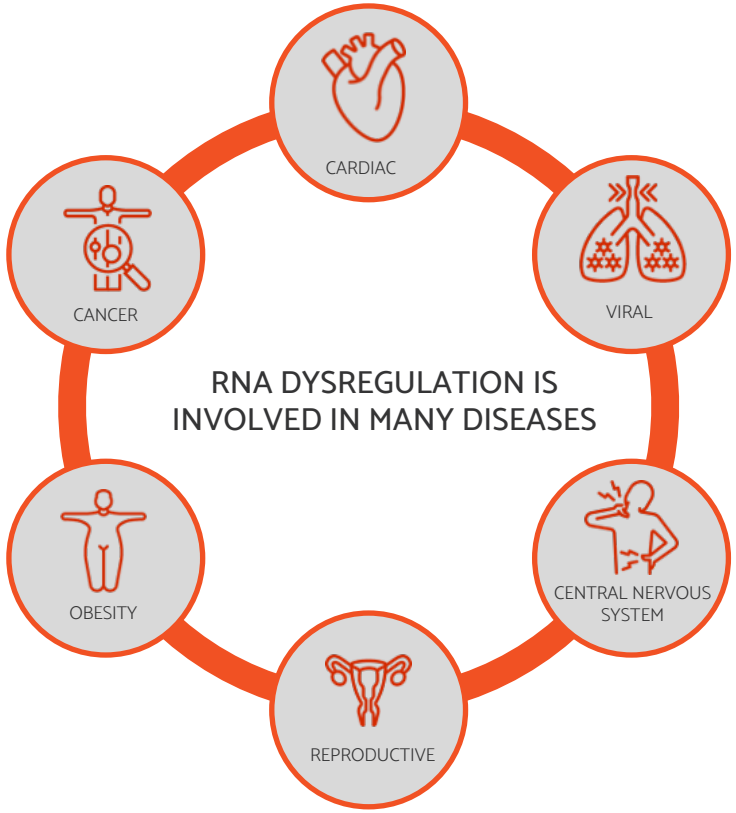
1. Triangle Insights (ASX Announcement: 14 April 2023)
2. Estimated number of patients that receive an anthracycline cycle in the USA each year – Triangle Insights
3. Primary market research conducted by Triangle Insights

m⁶A RNA dysregulation underlies many diseases

Ribonucleic acid (RNA) is the key information messenger that translates genetic instructions from DNA (genes) to cell proteins



Targeting RNA regulation pathways, like m⁶A methylation, may offer new treatment options for many diseases, including cancer



m⁶A RNA Opportunity

FTO – important role in human cancers?

Scientific discoveries over the last decade have identified dysregulation (loss of control) of RNA methylation as a key driver of cancer development[1]

Changes in m⁶A RNA methylation control the expression of key genes in cancer development and growth[2]

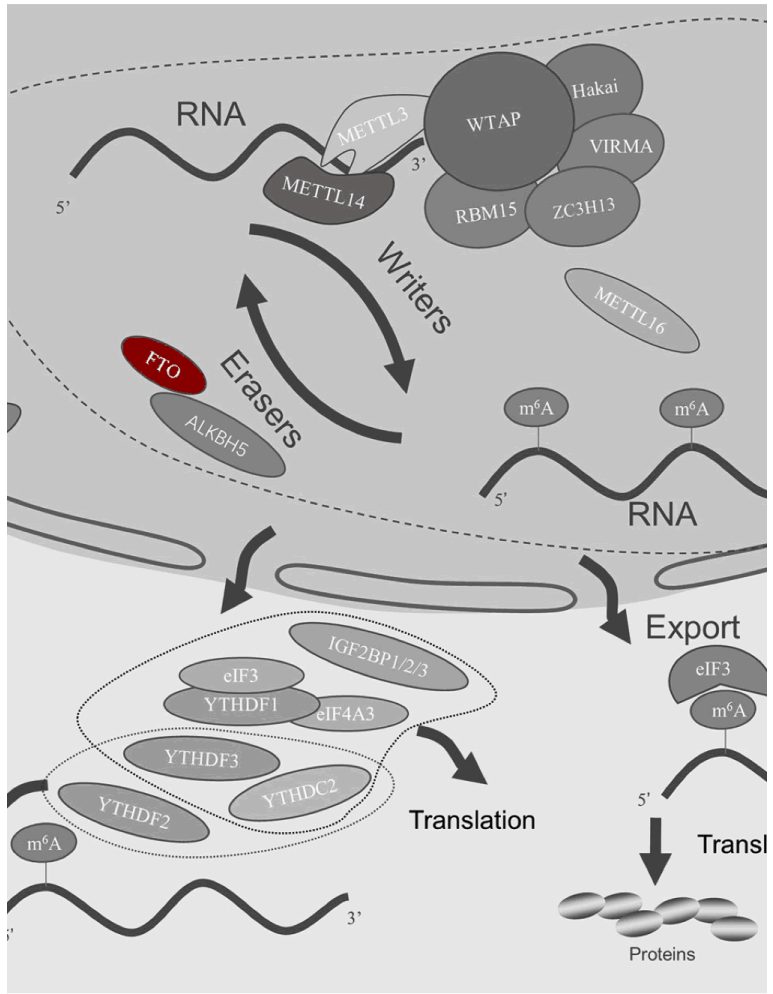
Fatso/ Fat mass- and obesity-associated Protein (FTO) is an m⁶A RNA demethylase that is involved in the control of m⁶A levels in mRNA[1]

Increases in the expression or activity of FTO are associated with cancer development and metastasis

Reductions in FTO expression or activity kills or slows the growth of a wide range of cancers including leukaemia, breast, lung, ovarian, gastric, brain, melanoma & pancreatic

Bisantrene has been independently reported to be a potent FTO inhibitor[3]

Despite rapid scientific progress, the clinical importance of m⁶A RNA and FTO as a cancer target is unknown due a lack of m⁶A targeted therapies



1. Deng, X., Su, R., Stanford, S., & Chen, J. (2018). Critical Enzymatic Functions of FTO in Obesity and Cancer. Frontiers in Endocrinology, 9, 724–7
2. Huang, H., Weng, H., & Chen, J. (2020). m⁶A Modification in Coding and Non-coding RNAs: Roles and Therapeutic Implications in Cancer. Cancer Cell, 37(3), 270–28
3. Su, R. et al. Targeting FTO Suppresses Cancer Stem Cell Maintenance and Immune Evasion. (2020) Cancer Cell 38, 79-96.e11.

FDA Fast Track & Breakthrough Designation

FDA Fast Track Designation (see Appendix)

More frequent communication with FDA

Eligibility for **Accelerated Approval** and **Priority Review**

Rolling Review of NDA

FDA Breakthrough Designation (see Appendix)

All Fast Track designation features

Intensive guidance on an efficient drug development program, beginning as early as Phase 1

Organisational commitment involving senior FDA managers

Example – Cosela®

An IV CDK 4/6 inhibitor designed to reduce the incidence of chemotherapy-induced myelosuppression in adult patients with extensive-stage small-cell lung cancer receiving chemotherapy[1]

2016 – Phase 1 safety study[2]

2017 – 2019 – 3x Phase 1b/2 trials[2]

2019 – Granted FDA Breakthrough Designation[1]

2020 – NDA submitted, received FDA Priority Review[1]

Feb 2021 – Granted FDA Accelerated Approval based on evidence from three (3) Phase 2 clinical trials with a total of 245 patients (only 123 treated with Cosela®) with newly diagnosed extensive-stage small-cell lung cancer receiving chemotherapy for the first time[1]

1. https://www.fda.gov/news-events/press-announcements/fda-approves-drug-reduce-bone-marrow-suppression-caused-chemotherapy
2. Daniel, D. et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial. Int J Cancer 148, 2557–2570 (2021).

RC220 cardioprotection clinical – benefits and goals

Leverages an Australian-focused Phase 1a/1b trial design

Phase 1a establishes optimal bisantrene anthracycline dosing and safety

Phase 1b generates proof-of-concept cardioprotection efficacy data in combination with anthracyclines

Highly cost effective

Trial will provide data on RC220 safety and cardioprotection proof–of-concept

Exploratory data generated on single-agent anticancer efficacy and the effects on the m^{6}A RNA system

Builds robust data set to support Phase 2 efficacy trials

Cardioprotection & m^{6}A RNA Phase 2 Trial[1]

A placebo-controlled, double-blinded, umbrella Bayesian combination trial of RC220. Focus on breast cancer plus any cancer or patient population that shows exceptional response to treatment in Phase 1

Size: 80-120 patients; up to 20 sites in Australia and internationally
Sponsor: Race Oncology
Primary endpoints: Cardioprotection assessed by standard & advanced cardiac markers including VO_2Peak
Secondary & exploratory endpoints: Anticancer efficacy & effect on m^{6}A RNA levels
Start: After completion of Phase 1
Timeline: 18-24 months due to Bayesian design uncertainty around total patient number (patient recruitment)

Generates gold-standard, double-blinded efficacy data of bisantrene as a cardioprotective agent and provides supportive data on anticancer efficacy & effect on m^{6}A RNA system

Trial uses same single-agent bisantrene 7-day lead-in dosing to generate robust clinical data on the effects of bisantrene on the m^{6}A RNA system and single-agent anticancer activity

Cost: A$32 million (based on 120 patients)

1. Fully funded assuming 75% or greater conversion of Piggyback Options in 2026

AML Phase 1/2 Investigator Initiated Trial[1]

A low intensity salvage treatment for patients unable or unwilling to tolerate high intensity chemotherapy who have failed standard of care AML treatments.

Size: 40-60 patients; up to 10 sites in Australia
Sponsor: Investigator
Primary endpoints: Safety & tolerability of bisantrene; Overall Response Rate
Exploratory endpoints: Event-free Survival; Overall Survival; Time to remission; Frailty scores; Time on treatment; Molecular response; Cardiac markers; Quality of Life
Start: Late H2 2024/early H1 2025
Timeline: 18-24 months recruitment + 2 year follow up; interim results in 24 months

Trial to use low dose bisantrene (RC220) in combination with oral decitabine (ASTX727) (Astex)

Trial will provide clinical efficacy data supporting the use of bisantrene in low intensity AML combination protocols that are compatible with standard of care use of venetoclax

Cost: A$4 million (based on 60 patients)[2]

1. Proposal as received from the Investigator in November 2023. May be subject to modification.
2. Fully funded from 75% or greater bonus option conversion in June 2024

FDA Fast Track Designation[1]

Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.

Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. AIDS, Alzheimer's, heart failure and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression and diabetes are also considered to be serious conditions.

Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy.

Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some advantage over available therapy, such as:

- Showing superior effectiveness, effect on serious outcomes or improved effect on serious outcomes
- Avoiding serious side effects of an available therapy
- Improving the diagnosis of a serious condition where early diagnosis results in an improved outcome
- **Decreasing a clinical significant toxicity of an available therapy that is common and causes discontinuation of treatment**
- Ability to address emerging or anticipated public health need

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers
- Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
- Rolling Review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA

1. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

FDA Breakthrough Therapy Designation[1]

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- **A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy**

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1
- Organizational commitment involving senior managers

1. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

VO_2Peak Measures of Cardiac Damage

Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) have been the standard of care measures for evaluating chemotherapy-associated cardiotoxicity

VO_2Peak can be simply assessed in minutes using a continuous ramp protocol on an upright cycle ergometer while measuring the volume of oxygen consumption and expired carbon dioxide[1]

A VO_2Peak below 18mL/kg/min has been termed 'functional disability' because a level below this prevents patients performing basic daily living activities and is associated with a seven- to nine-fold increased risk of heart failure[2]

The American Heart Association has endorsed the measurement of VO_2Peak defined functional disability as an important clinical endpoint for older adults with or at risk for cardiovascular disease (CVD)[3]

Recent research from the Baker Institute in 206 cancer patients[1] has found that changes in LVEF or GLS are not strongly correlated with short-term symptoms, functional capacity, or long-term heart failure (HF) risk

Anthracycline exposure was found to reduce average VO_2Peak in patients by 8-11% (equivalent of 8 to 11 years of normal ageing) with the rates of functional disability near doubled (15% vs. 26%). In contrast, only small reductions in LVEF (59% vs. 58%) and GLS (-19.4 vs. -18.9) were observed in the same treated cohort

Importantly, 43% of the anthracycline exposure patients experienced a 10% or greater reduction in VO_2Peak which enables the detection of significant changes in small trials (~30 patients)

1. Howden, E. J. et al. Traditional markers of cardiac toxicity fail to detect marked reductions in cardiorespiratory fitness among cancer patients undergoing anti-cancer treatment. Eur. Hear. J. - Cardiovasc. Imaging 22, 451–458 (2021).
2. Forman, D. E. et al. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals From the American Heart Association. Circulation 135:e894–918 (2017).
3. Khan, H. et al. Cardiorespiratory fitness and risk of heart failure: a population-based follow-up study. Eur J Heart Fail 16:180–8 (2014).