ASX Announcement

Race Submits Human Ethics Application to Commence Cardioprotection Breast Cancer Trial

- **Ethics request submitted to commence the lead in observational stage of a subsequent interventional Phase 1/2b cardioprotection clinical program using Zantrene**
- **Observation trial is the first step in advancing the cardioprotection opportunity for Zantrene in the clinic.**

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9 December 2022 – Race Oncology Limited ("Race") is pleased to announce it has submitted a human ethics application to the Hunter New England Human Research Ethics Committee (NSW, Australia) seeking approval to commence the observational stage of a planned Phase 1/2b clinical trial of Zantrene® (bisantrene dihydrochloride) in breast cancer patients to be treated with doxorubicin and cyclophosphamide and who have two or more cardiovascular risk factors.

This study will be led by Associate Professor Aaron Svedlov, a highly credentialed cardiologist with a research focus on cardio-oncology. Dr Sverdlov was awarded the 2018 Ministerial Award for Rising Stars in Cardiovascular Research. He established and co-chairs the National Cardio-Oncology Working Group under the auspices of the Australian Cardiovascular Alliance. Dr Sverdlov has over 50 peer-reviewed publications and four book chapters in the field of cardio-oncology.

The study will recruit and monitor up to 50 patients being treated for breast cancer using the standard of care (SoC) regimen of doxorubicin (Adriamycin®) and cyclophosphamide - referred to as "AC chemotherapy". The aim of this study is to identify the rate and level of heart damage caused by AC chemotherapy using modern advanced cardiac imaging and biochemical methods. In addition, the anti-cancer efficacy of AC chemotherapy will be monitored using a liquid biopsy (DNA) approach. The study is expected to fully recruit in 2023.

The data from this study will be used to design a subsequent Phase 1/2b interventional trial that may help patients to avoid the permeant heart damage caused by AC chemotherapy and improve anti-cancer outcomes. These human trials are fully funded from capital raised in December 2021 (ASX Announcement: 21 December 2021).

Race CEO Phillip Lynch commented, *"Cardioprotection remains a significant unmet patient need, and our preclinical data suggests that we have in Zantrene the opportunity to effectively address this need. I look forward to us progressing the clinical program and to clarifying the large commercial opportunity this program represents."*

Race CSO Dr Daniel Tillett commented, *"This trial is Race's first step in advancing the cardioprotection opportunity for Zantrene in the clinic. Gaining high quality observational data to design our interventional Phase 1/2b trial of Zantrene in breast cancer is critical to the success of this program. We look forward to updating our investors on the progress of this trial."*

Trial Background

Anthracycline Chemotherapeutics

Anthracyclines are one of the most effective anti-cancer treatments developed and are used in more cancer settings than any other class of chemotherapeutic agent.[1] These drugs are used to treat millions of cancer patients every year, including those with leukemias, lymphomas, neuroblastoma, kidney, liver, stomach, uterine, thyroid, ovarian, sarcomas, bladder, lung and breast cancers. The most clinically used anthracyclines are doxorubicin, daunorubicin, epirubicin and idarubicin.[2]

The anti-cancer efficacy of anthracyclines is known to correlate to dose with higher doses providing greater efficacy, but at the expense of higher rates of serious and irreversible side-effects.[1] In clinical practice, anthracycline chemotherapeutics such as doxorubicin are given at a level close to the patient's maximal tolerated dose (MTD) in order to maximise the anticancer efficacy. Common dose limiting toxic side-effects of anthracyclines include: cardiotoxicity, suppression of the immune system and red blood cell production (myelosuppression), hair loss (alopecia), and gastrointestinal toxicity that can cause serious nausea and weight loss.[1,2]

Anthracycline Cardiotoxicity

While highly effective anti-cancer drugs, the anthracyclines can cause serious and permanent damage to the heart in many patients. Some studies have estimated that over half of patients exposed to anthracyclines will develop some form of heart disease within 6 years of treatment.[3]

Anthracyclines, such as doxorubicin and epirubicin (Figure 1), can lead to either acute or late onset cardiotoxicity. Acute toxicity is associated with increased inflammation and can lead to a pericarditis-myocarditis syndrome. Flaccid dilative cardiomyopathy is the predominant form of late onset anthracycline cardiotoxicity and can occur months to years after anthracycline exposure.[4]

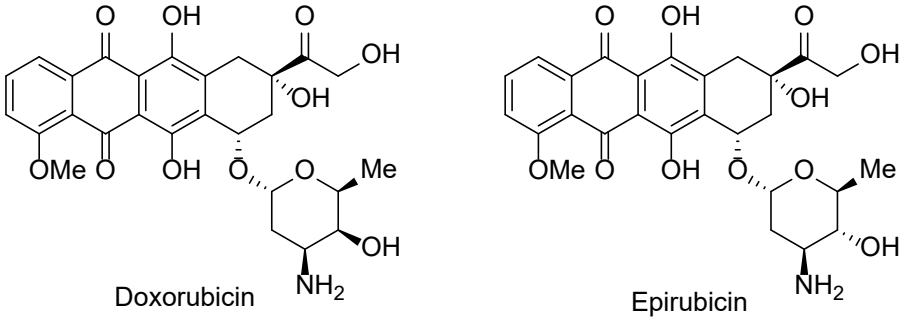

Figure 1. Chemical structures of the anthracyclines, doxorubicin and epirubicin.

Although the mechanism of early and late onset anthracycline cardiotoxicity remains unclear, risk factors include increased cumulative anthracycline dose, concurrent mediastinal radiation, extremes of age, female gender, and pre-existing heart disease.[5]

Prevention of Anthracycline Cardiotoxicity

A number of potential cardioprotective techniques and therapies have been explored over the years, ranging from modified anthracycline preparations, anti-oxidants, free radical scavengers, renin-angiotensin-system antagonists, cardio-selective beta-blockers to statins. While many showed promise in animal studies, clinical studies have often had mixed results with many agents offering little or no cardio-protective benefit and/or compromising the cancer treatment.[6] None have offered the combined features of cardioprotection and improved anti-cancer efficacy.

As a consequence, cardioprotective treatments are not routinely used in clinical oncology practice. Indeed, there remains clear demand for treatment options that prevent today's cancer patient from becoming tomorrow's cardiac patient, all while extending anti-cancer effect.

Anthracycline use in Breast Cancer

Breast cancer accounts for 30% of all new cancer diagnoses in women. It is estimated in the US that in 2022, 287,850 new cases of invasive breast cancer are expected to be diagnosed in women, along with 51,400 new cases of non-invasive (*in situ*) breast cancer.[7] The vast majority (94%) of new breast cancer patients present with early-stage disease.[8]

Anthracycline agents such as doxorubicin and epirubicin, are routinely used for the management of breast cancer with follow-up taxane-based therapy.

Surprisingly, women diagnosed with early-stage breast cancer were found to be more likely to die from cardiovascular disease than from breast cancer. Cardiovascular disease is also the leading cause of death in women over 75 diagnosed with stage II breast cancer.[9]

The risk of cardiotoxic damage is so elevated in breast cancer patients that many oncologists have moved in recent years to using anthracycline-free treatment regimens or limiting patient dosages, despite the well-established efficacy of anthracyclines.[9]

Zantrene Cardioprotection

Zantrene was originally developed as a heart safer alternative to the anthracyclines particularly with respect to preservation of heart muscle.[10]

In the late 1980s, Zantrene was the subject of a US based Phase 3 single agent clinical trial in advanced breast cancer patients. This Phase 3 trial showed that Zantrene had comparable efficacy to standard of care treatment, doxorubicin, but was associated with significantly less damage to the patients' hearts. Approximately 24% of patients who received doxorubicin suffered serious heart failure compared to just 6.6% with Zantrene.[11]

In recent studies, Zantrene was found to protect human heart cardiomyocytes (heart muscle cells) grown in cell culture from doxorubicin-induced cell death (ASX Announcement: 22 November 2021). It was also found to protect the hearts of mice from the damaging effects of doxorubicin even when the chemotherapeutic dose was increased without significant additional toxicity or bone marrow suppression (ASX Announcement: 30 June 2022).

Cardioprotection Clinical Trial Design

This first study (Stage 1) is observational in nature and designed to assess the prevalence of cardiac toxicity (sub-clinical and clinical) in a cohort of cardiovascular high-risk breast cancer patients receiving doxorubicin/cyclophosphamide (AC) chemotherapy. Data from this study will be used to inform and power a subsequent interventional clinical trial (Stage 2) with the objective of using Zantrene in combination with AC to prevent cardiac damage and increase anti-cancer efficacy (Figure 2).

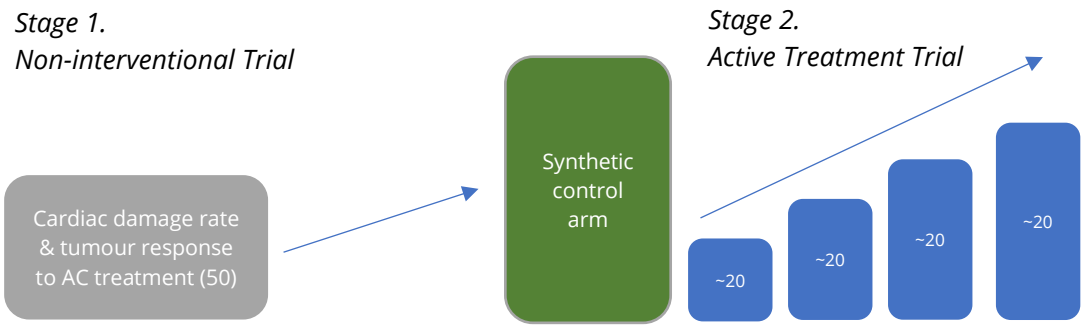

Figure 2. Two stage cardioprotection trial design. Stage 1 is an observational trial to determine the rate and level of cardiac damage from AC chemotherapy. Stage 2 is an interventional study where increasing levels of Zantrene are used to determine the optimal dose to minimise heart damage and provide anti-cancer efficacy.

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Stage 1. Clinical Trial Summary

Study Title	A non-interventional study to establish the incidence and extent of chemotherapy-induced cardiotoxicity in breast cancer patients at high cardiovascular risk receiving doxorubicin / cyclophosphamide (AC) therapy.
Phase of Development	Observational
Active Ingredient	Doxorubicin & cyclophosphamide
Study Description	Detection of chemotherapy induced cardiotoxicity in breast cancer patients.
Principle Investigator	A/Prof Aaron Svedlov
Sponsor	Race Oncology
Indication/population	≥18 years of age with breast cancer and least 2 cardiac (per HFA-ICOS risk assessment score) risk factors who have been prescribed doxorubicin / cyclophosphamide chemotherapy for at least 4 cycles.
Number of Subjects	Up to 50 patients
Study Period	24 months
Study Design	An observation study of the rate and extent of clinical and sub-clinical cardiac damage in breast cancer patients with multiple pre-existing cardiac risk factors as well as the cancer response rate.
Statistical Methods	Assuming a 15% cardiotoxicity rate (>11% decrease in global longitudinal strain by conventional echocardiographic measurements) 47 patients would be required using an alpha of 0.05 and power of 80%.
End Points	**Primary:** Incidence, severity and biomarkers of early, sub-clinical and clinical cardiotoxicity in breast cancer patients treated with AC chemotherapy. **Secondary:** Clinical safety profile of AC treatment in the patient population. Cancer response to AC treatment. Frequency, severity of alopecia (hair loss). Impact of AC treatment on overall patient quality of life.
Participating Centres	Calvary Mater Hospital, Newcastle, NSW.

Q&A

Why study breast cancer patients getting standard of care doxorubicin / cyclophosphamide (AC) chemotherapy?

While the rate of clinical heart damage (>10% decrease in heart output) from AC chemotherapy is known from the scientific literature, the rate and level of sub-clinical heart damage has not been well described. Since sub-clinical heart damage has historically been considered an unavoidable aspect of chemotherapy, its rate and level have often not been collected at the level of precision required to construct a reliable synthetic control arm. In addition, new technology and imaging techniques now allow cardiac damage to be detected much more accurately and at lower levels than in the past.

Knowing the true rate and level of chemotherapy induced heart damage will allow the interventional cardioprotective trial to be optimised, ensuring the minimum number of patients will be exposed to potentially ineffective doses of Zantrene.

What are synthetic control arms?

Synthetic control arms use real-world evidence to support interventional clinical trials. Instead of collecting clinical data from patients recruited for a trial who have been randomly assigned to a control or standard-of-care (SoC) arm, synthetic control arms model the experimental treatment controls using real-world data that has previously been collected from other sources such as health data generated during routine care, electronic health records, administrative claims data, disease registries, and/or other clinical trials[12].

Synthetic control arms may reduce or eliminate the need to enrol control or standard-of-care participants in an active (interventional) trial, which can increase efficiency, reduce delays, lower trial costs, and speed the approval of life saving therapies. For example, if a trial needs to have 300 patients in the treatment arm in order to demonstrate the efficacy of a new drug, then instead of having to recruit 600 patients – 300 for the active arm and 300 for the control arm – only 300 patients may need to be recruited when using a synthetic control arm design.

The major limitation of synthetic control arms is they require that the disease is predictable and that the standard of care is well-defined and stable. Fortunately, AC chemotherapy in breast cancer meets these two requirements.

What are the advantages of this two-trial approach?

By splitting the cardioprotection trial into two separate trials (observational and interventional) we can achieve the following outcomes:

1. The study can begin in Q1 2023 without the need for the new formulation to be manufactured and be ready for clinical trial. This will speed the time to completion of the full cardioprotection program.
2. The treatment cohort can be sized appropriately to ensure the minimum of patients are exposed to sub-optimal or excessive doses of Zantrene.

3. Patients do not need to be randomly assigned to a placebo control arm in the Phase 1 interventional trial, increasing patient satisfaction and participation.
4. The cost of the trial is reduced as a separate observational study is cheaper to run than a conventional control arm in an interventional trial.

How long will the human ethics approval process take?

This is difficult to answer as it depends on many factors outside of Race's control. Our expectation is that as this first observational study has minimal additional risks to the patients, it will receive approval relatively promptly allowing the trial to start in Q1 2023.

When will the first patients be treated with Zantrene to protect their hearts during chemotherapy?

The aim is to treat the first breast cancer patient with Zantrene soon after the new formulation has been manufactured and is ready for use in clinical trials – Race expects this to occur in Q3 2023 (ASX Announcement: 28 September 2022).

References

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About Race Oncology (ASX: RAC)

Race Oncology is an ASX listed precision oncology company with a Phase 2/3 cancer drug called Zantrene®.

Zantrene is a potent inhibitor of the Fatso/Fat mass and obesity associated (FTO) protein. Overexpression of FTO has been shown to be the genetic driver of a diverse range of cancers. Race is exploring the use of Zantrene as a new therapy for melanoma and clear cell renal cell carcinoma, which are both frequent FTO over-expressing cancers.

In breakthrough preclinical research, Race has also discovered that Zantrene protects from anthracycline-induced heart damage, while in tandem acting with anthracyclines and proteasome inhibitors to improve their ability to target cancer.

The Company also has compelling clinical data for Zantrene as a chemotherapeutic agent and is in multiple clinical trials in Acute Myeloid Leukaemia (AML).

Race is pursuing outsized commercial returns for shareholders via its 'Three Pillar' strategy for the clinical development of Zantrene. Learn more at www.raceoncology.com

If you have any questions on this announcement or any past Race Oncology announcements, please go to the Interactive Announcements page in our Investor Hub here: https://announcements.raceoncology.com.

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