RACE ONCOLOGY

ASX Announcement

Primary Anticancer Mechanism of Action of (E,E)-bisantrene discovered to be from binding to G4-DNA and RNA sites

- (E,E)-bisantrene (RCDS1) discovered act by binding to G4-DNA & RNA structures and is not a doxorubicin-like chemotherapeutic
- Targeting G4-DNA & RNA reduces the activity of many important cancer genes (including the master gene regulator *MYC)*, inhibits topoisomerase 2 and telomerase, and indirectly increases the level of m^6A in RNA
- The discovery of the G4-targeting mechanism of action of RCDS1 has important clinical and commercial implications.

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2 October 2025 – Race Oncology Limited ("Race") is pleased to announce the discovery of the primary mechanism of action (MOA) of (E,E)-bisantrene (RCDS1). Scientific studies undertaken by Race Oncology and collaborators have identified the anticancer activity of RCDS1 predominantly results from binding and stabilising of important regulatory DNA and RNA structures called G-quadruplexes (G4) which found throughout the human genome (Figure 1). G4 sequences form 3-dimensional structures that regulate the expression and translation of many genes involved in causing cancer (oncogenes), including the master cancer growth regulator, *MYC*. In addition, the stabilisation of G4-DNA and RNA structures inhibits the enzymes topoisomerase 2 and telomerase, and indirectly increases the level of m^6A in RNA, mimicing the enzymatic inhibition of the fat mass and obesity-associated protein (FTO).

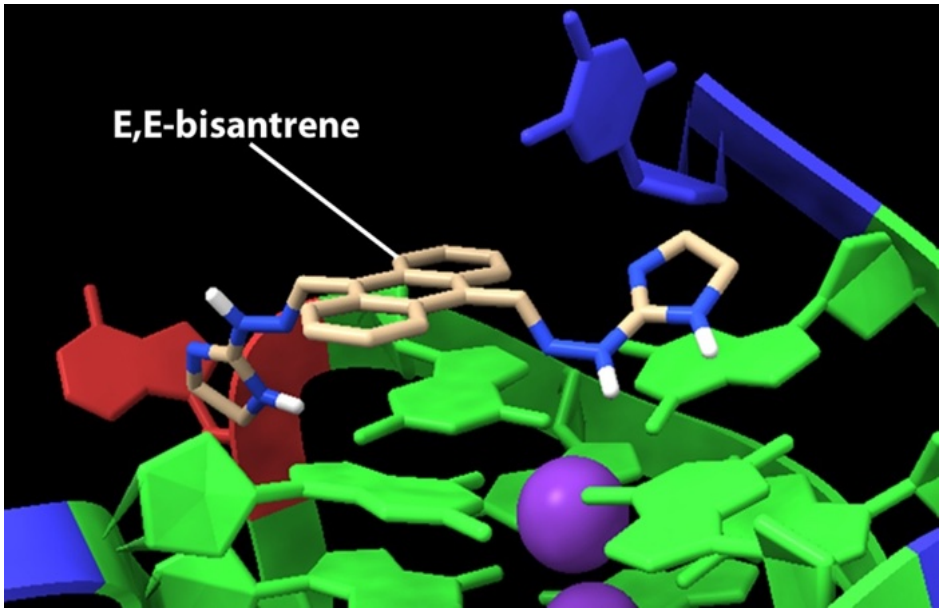

Figure 1. Model of RCDS1 (E,E-bisantrene) binding to the G4 DNA structure found within the promotor region of *MYC*.

Race Oncology CEO and Managing Director, Dr Daniel Tillett commented, *"The discovery (E,E)-bisantrene acts primarily by binding to G4-DNA and RNA structures, and not like the chemotherapeutic doxorubicin, fundamentally changes our thinking on how to best use this drug in the clinic. Bisantrene continues to surprise, and we look forward to building on this mechanism of action discovery in our future clinical and commercial plans."*

Prior assumed mechanism of action of bisantrene

Bisantrene has long been assumed to be a DNA targeting chemotherapeutic anticancer drug like the widely used anthracyclines (e.g. doxorubicin). There was little data to support this hypothesis beyond early studies showing bisantrene binds to double-stranded DNA and inhibits DNA replication and RNA transcription[1]. While it was noted in the scientific literature that bisantrene behaved differently to the anthracyclines (most notably in causing minimal-to-no cardiotoxicity), the limited understanding of how all anticancer drugs worked at a molecular level in the 1980s made determining the true MOA of bisantrene difficult[2]. The conclusion of the clinical development of bisantrene by Lederle Laboratories in 1988 effectively ended most scientific interest in studying how bisantrene works as an anticancer agent.

New studies into the molecular mechanism of action of (E,E)-bisantrene

Race Oncology began an active program to explore how (E,E)-bisantrene works using modern science. In the first stage, RCDS1 was studied across a large and diverse panel of cancer cells using an extensive array of both historical and modern anticancer drugs. The rationale for this analysis is that mechanistically similar drugs cluster together, enabling an unbiased grouping of a drugs by mechanism of action. As shown in Figure 2, RCDS1 did not cluster with the well-known anthracyclines, but instead aligned with a range of unexpected drugs, including the G4-DNA binding agent, actinomycin D.

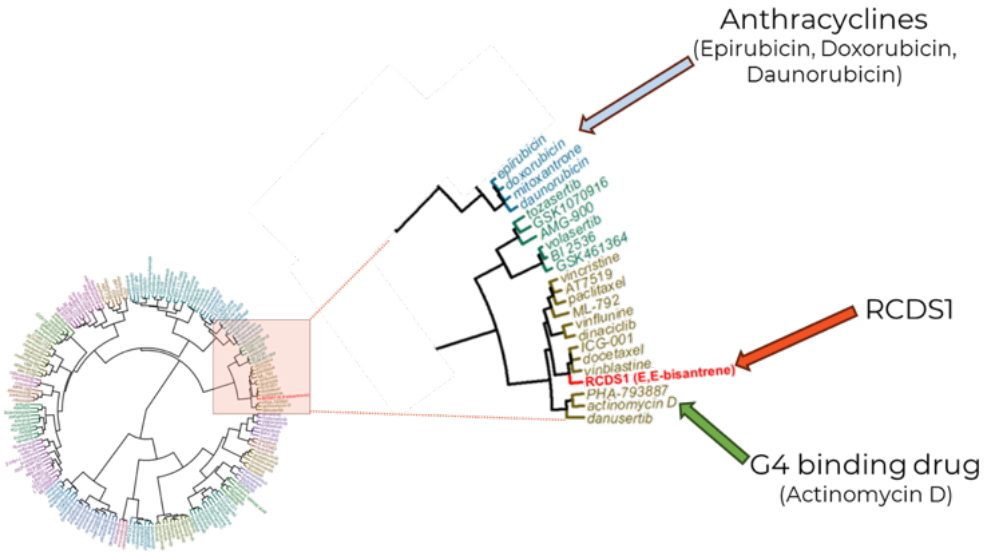

Figure 2. Cluster analysis of the anticancer responses of 195 drugs across 102 cancer cell lines showing that RCDS1 (E,E-bisantrene) is similar in mechanism of action to the G4-DNA binding drug actinomycin D.

This early result, together with an extensive review of the scientific literature, led Race to initiate a series of studies exploring the binding of RCDS1 to G4-DNA and RNA regions and downstream anticancer effects.

Primary mechanism of action of (E,E)-bisantrene discovered to be via G4-DNA and RNA binding

The Race preclinical team and other investigators[3] uncovered G4-binding drugs like RCDS1 exert their anticancer activity through a range of downstream effects including: inhibiting telomerase[4], inhibiting topoisomerase II and generating double-stranded DNA breaks[5], DNA hypomethylation[6], increasing m^6A levels in RNA, and reducing the activity of many important cancer genes such as *MYC* (Figures 3 & 5).

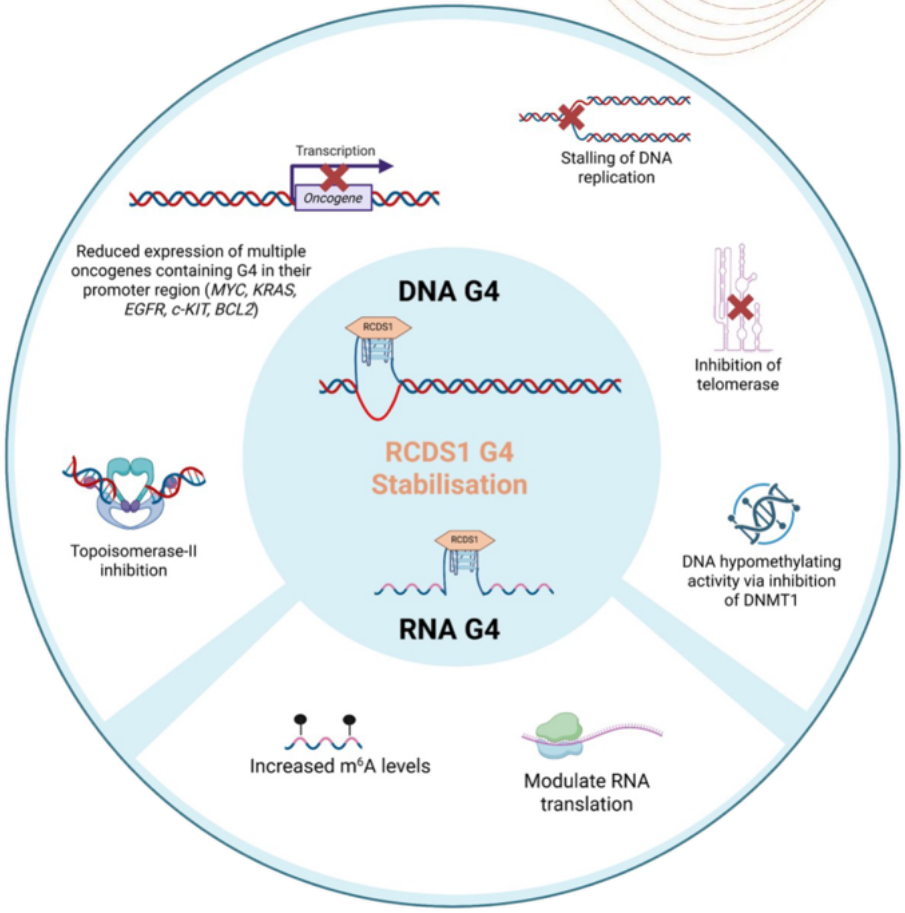

Figure 3. Binding of RCDS1 to G4-DNA and RNA structures causes multiple downstream anticancer effects.

This broad activity is shared with other G4-DNA binding drugs which are known to regulate the expression of cancer genes that contain G-quadruplex within their promoter regions, including *MYC*, *c-KIT*, *KRAS*, *TERT*, *EGFR*, *BCL2*, *VEGF*, *HIF1A*, *MYB* and *PDGFA* (reviewed in Collie *et al.*).[7]

Importance of MYC in cancer growth and progression

The MYC protein acts as a master switch that controls the expression of many genes involved in a myriad of physiological processes, such as cell growth, differentiation, survival, metabolic reprogramming, cell adhesion, angiogenesis, chemotherapy resistance, and immune surveillance.[8] The *MYC* gene is genetically activated and/or overexpressed through gene amplification, chromosomal translocation, or mutation in over 70% of human cancers, making it a central driver of cancer growth, therapy resistance, and proliferation.[9]

Despite extensive efforts from the pharmaceutical industry to target MYC directly with small molecule drugs, this has proven an intractable challenge because the important functional domains of MYC protein are intrinsically disordered and lack a targetable active site. In addition, the high affinity interaction between MYC and its obligate protein binding partner MAX, along with the partial functional redundancy of the different MYC family members and their nuclear localisation, have posed an enduring obstacle for the development of effective MYC-inhibiting cancer drugs.[10]

The *MYC* gene promoter region contains one of the most extensively studied DNA G-quadruplexes. Hurley and coworkers first reported *MYC* gene expression can be greatly decreased by the binding of a G-quadruplex stabilising small molecule ligand.[11] Additional G-quadruplex binding ligands have since been shown to reduce *MYC* gene expression, overcome anticancer therapy resistance, and slow cancer cell growth (Figure 4).[12,13]

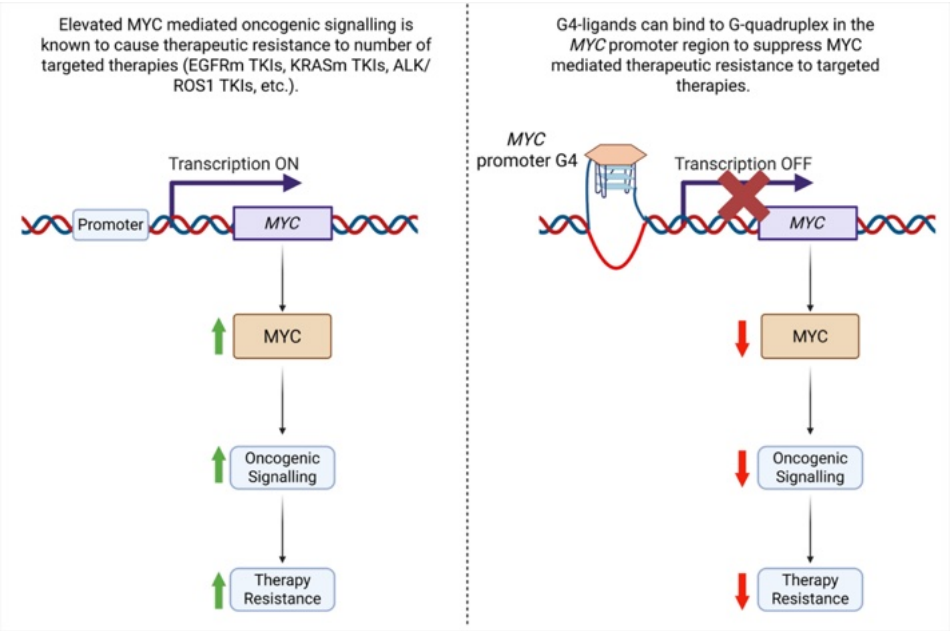

Figure 4. Ligand binding to the *MYC* gene G4 promoter region causes a downregulation of MYC expression resulting in reduced oncogenic signalling, cancer growth and anticancer therapy resistance.

Importantly, studies conducted by Race have found that potent downregulation of the *MYC* gene occurs shortly after treatment with RCDS1 (Figure 5). This MYC-targeting has also been observed in other cancer cell types.[14]

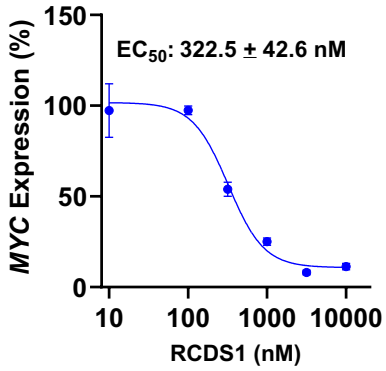

Figure 5. Expression of the *MYC* gene is dose-dependently downregulated by RCDS1 in MDA-MB-231 breast cancer cells.

G-quadruplexes and the m^{6}A RNA regulatory system

The level of the modified nucleotide m^{6}A in RNA has been found to play an important role in a wide range of diseases, such as obesity, heart disease, type 2 diabetes and cancer.[15] Cellular m^{6}A RNA levels are regulated by the relative activities of the METTL3/METTL14 m^{6}A RNA methylase complex (m^{6}A writers) and the FTO and ALKBH5 m^{6}A RNA demethylation enzymes (m^{6}A erasers)(Figure 6).[16] While a complex and still developing field, decreases in m^{6}A levels have been associated with cancer treatment resistance and disease aggressiveness.[17]

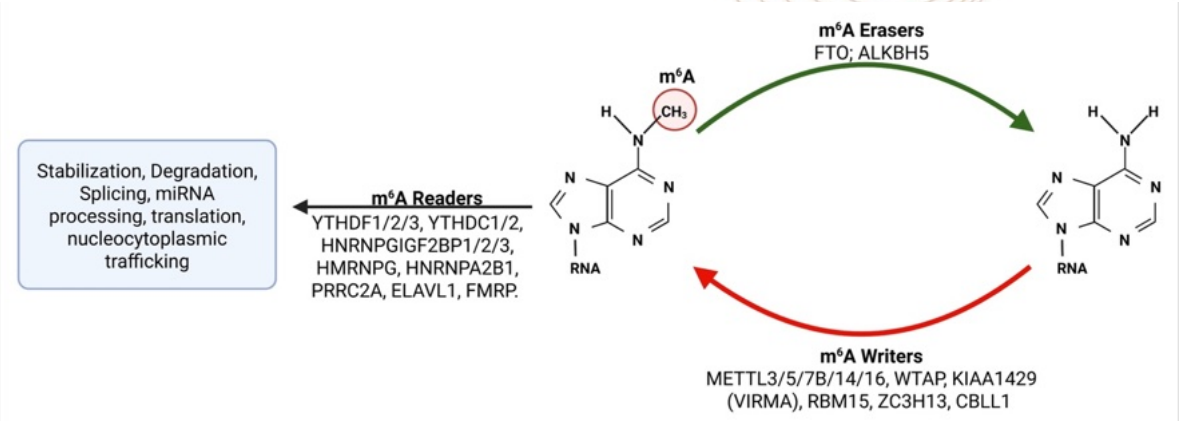

Figure 6. Levels of m⁶A in RNA provide multifaceted regulation of gene expression. m⁶A levels affect transcription, alternative splicing, alternative polyadenylation, nuclear export, cap-dependent and cap-independent translation, mRNA degradation, and mRNA stabilisation. A diverse set of reader proteins that selectively bind m⁶A, either directly or indirectly, mediate the many effects on gene expression.

Intriguingly, G-quadruplexes have been found to indirectly regulate the levels of m⁶A in RNA via two separate mechanisms. Firstly, the expression of *FTO* and *ALKBH5* is regulated by MYC, such that downregulation of MYC reduces the expression of these two demethylases, leading to a corresponding increase in RNA m⁶A levels and vice versa.[18]

Secondly, the binding of the METTL3/METTL14 methylation complex to RNA is controlled by G4-RNA sites within RNA transcripts. Molecules that increase the stability of G4-RNA structures increase the binding of the methylation complex to RNA, and hence the methylation rate and level of m⁶A found in RNA.[19]

Importantly, both these indirect mechanisms can mimic at a cellular level the increases in m⁶A that are seen from direct enzymatic inhibition of the RNA demethylases FTO and ALKBH5.

Clinical & commercial significance

The discovery of the primary anticancer mechanism of action of RCDS1 provides several benefits. Knowing how an anticancer drug works at the molecular level makes it much simpler to identify the cancer types (or sub-types) that are most likely to respond to the drug. This knowledge extends to aiding the identification of drug combinations that are likely to be synergistic when used together. Rather than having to blindly test millions of possible combinations of different drugs in hundreds of cancer types, knowing the MOA allows the rational selection of the likely best drug combinations and cancers to treat. Regulators prefer the MOA of new drugs to be included in regulatory submissions since it improves patient safety by helping predict side effects, guides appropriate use, and identifies the patients most likely to benefit.

An important additional benefit to knowing the MOA of RCDS1 is it enables the development of pharmacodynamic biomarker tests that are predictive of a patient's response to treatment. New cancer drugs with an associated biomarker test are more than twice as likely to obtain regulatory approval.[20]

Finally, understanding the MOA of a drug increases the probability of successful pharma partnering – put simply, large pharma has an expectation that their partners understand how any new drug works because this reduces scientific and clinical risk, improves trial design, and aligns with regulatory expectations.

Next steps

- Additional preclinical studies exploring the G4-DNA and RNA binding effects of RCDS1 on anticancer efficacy and treatment resistance modification.
- Further investigations to identify the major cancer indication(s) most suited to RCDS1 use and the best drug combinations to explore in the clinic.
- Identification of the most valuable commercial market opportunity for RCDS1 and the clinical trials required.
- Publication of the mechanism of actions studies in peer reviewed scientific journals and/or presentation at major international conferences.

Race management will host a webinar explaining the significance of this discovery on Wednesday, 8 October, 2025 at 6 pm AEST. To register for this webinar please use the following link:

https://us02web.zoom.us/webinar/register/WN_mZs08BT8SDC4V9I2eTLbgA

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Q&A

Why did it take Race so long to discover (E,E)-bisantrene (RCDS1) was a G4-binding drug?

Science is hard. The anticancer effects of RCDS1 are varied and highly complex, making identification of the underlying mechanism of action neither easy nor straightforward. The last 40 years have seen massive advances in molecular biology and cancer research and have enabled what was an impossible task in the 1980s to be possible today. A contributing factor is that the significant resources required to understand the mechanism of action of RCDS1 were only committed by Race in the last couple of years.

The model of RCDS1 bound to the G4-DNA structure shows the molecule in the (E,E)-configuration. Is this why only the (E,E)-bisantrene isomer is active?

Excellent question. The answer is we don't know yet why the (E,Z)-form of bisantrene has little to no anticancer activity, but the idea that the (E,Z)-isomer could have reduced binding to G4-structures from the orientation of the Z-side chain is plausible. This hypothesis is currently being explored by the Race team and collaborators.

What is MYC? Why is it important in cancer?

MYC acts as a master on-off switch for cell growth and division, activating the production of numerous proteins that drive the cell to divide. In normal cells, the job of MYC is to help control how quickly cells grow, copy their DNA, and divide. It is tightly regulated, turning on only when the body needs new cells for growth, repair, or immune responses, and switches off when it is no longer needed.

In cancer, MYC becomes overactive, and regulation is lost. As a result, MYC drives cancer cells to divide uncontrollably and alters their metabolism to support rapid tumour growth. MYC is overexpressed or dysregulated in around 70% of cancers making it one of the most important targets for new anticancer treatments.

Why are there no drugs that specifically target MYC in the clinic?

MYC has been considered undruggable despite decades of research conducted by the pharmaceutical industry. In general, most successful drugs bind to specific pockets that exist in the target protein structure, much like how a key fits into a lock. The functional parts of the MYC protein are unstructured and lack drug binding pockets. This has hampered efforts to find potent MYC-inhibiting drugs despite a great deal of scientific effort.

Are there other G-quadruplex binding drugs?

Yes, but only a few. To bind to a G-quadruplex structure well, molecules must have a flat aromatic core structure with charged and flexible side groups. Unfortunately, such structures often confer poor drug-like properties (e.g. solubility, pharmacokinetics, tissue distribution etc.). Indeed poor solubility was a major problem with bisantrene since the 1980s and only extensive efforts by Race to develop the RC220 formulation made it a viable drug.

The two best known G-quadruplex drugs in the clinic are CX-5461 (pidnarulex) and QN-302. Both are only in early clinical development for oncology indications.

Are all G-quadruplex binding drugs similar in activity?

No. There are more than 80 different G-quadruplex structures known depending on the DNA or RNA sequences from which they are formed. Each G4-targteting drug binds to only a subset of the possible G4-structures found in the human genome, resulting in a wide variation in activity of the different drugs.

Why has nothing been mentioned about the cardioprotection mechanism of action in this announcement?

This announcement is an update on discoveries made into the anticancer mechanism of action of RCDS1, not its cardioprotective properties. Additional data will be presented by Race CEO Dr Daniel Tillett at the European Society of Medical Oncology (ESMO) Annual Conference being held from the 18th to 21st of October 2025. Shareholders can expect further announcements after this work is presented at ESMO.

Is there a video explaining these amazing discoveries?

Yes. Dr Pete Smith, Race Executive Chair, has recorded a short video which is available on the Race Investor Hub pages: https://announcements.raceoncology.com/link/PGqJze

Please summarise all this complex science. What do I really need to know?

There are three key takeaways from this announcement.

1. We now know how RCDS1 works as an anticancer drug – it isn't an old chemo drug like doxorubicin.
2. Knowing how RCDS1 works allows us to find the best possible uses for RC220 and help more cancer patients sooner.
3. The potent effects of RCDS1 on the master cancer growth regulator MYC is very important, both clinically and commercially.

About Race Oncology (ASX: RAC)

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

Race's lead asset, RCDS1 (E,E-bisantrene), is a small molecule anticancer agent primarily functioning via G4-binding. RCDS1 has demonstrated therapeutic activity in cancer patients with a well characterised safety profile.

Race is advancing a proprietary formulation of RCDS1 (RC220) to address the high unmet needs of patients across multiple oncology indications, with a clinical focus on combinations with an anthracycline (doxorubicin), where we aim to deliver both cardioprotection and enhanced anticancer activity in solid tumour indications. Race is also exploring the use of RC220 as a low intensity treatment for acute myeloid leukaemia and other cancers.

Race Oncology has collaborated with Astex, MD Anderson, Sheba City of Health, UNC School of Medicine, University of Wollongong and University of Newcastle, and is actively exploring partnerships, licence agreements or a commercial merger and acquisition to accelerate access to RC220 for patients with cancer across the world.

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 announcements.raceoncology.com

Race encourages all investors to go paperless by registering their details with the Company's share registry, Automic Registry Services, at www.automicgroup.com.au.

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