ASX Announcement

Race Receives Human Ethics Approval and Submits Governance Application for Extramedullary AML & MDS Trial

- **Human ethics approval received for the lead site in Race's clinical trial of Zantrene for the treatment of patients with extramedullary AML and high risk MDS**
- **Research Governance Office approval expected in coming weeks in advance of the first patient being enrolled in the study**
- **The first clinical trial in the world to investigate the targeting of FTO as a potential cancer therapy using an AML & MDS population.**

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6 April 2022 – Race Oncology Limited ("Race") is pleased to announce it has received human ethics approval for its open label clinical trial of Zantrene® (bisantrene dihydrochloride) in patients with extramedullary Acute Myeloid Leukaemia (AML) or high-risk Myelodysplastic Syndrome (MDS).

Before patients can be enrolled and treated at the lead site - Calvary Mater Newcastle Hospital - Race must receive Research Governance Office (RGO) (site budget and contracting) approval. All required documentation has now been submitted to enable this outcome. Governance approval is typically received within 4 to 8 weeks from submission.

This open label Phase 1 trial with a dose expansion Phase 2 stage will recruit up to 60 patients with extramedullary AML or MDS using a two-stratum (arm) design (ASX Announcement: November 1, 2021).

Extramedullary AML

Extramedullary AML occurs when the leukaemia spreads from the bone marrow and forms solid tumours in tissues such as the skin, breast, kidney, brain and others. A 2020 prospective positron imaging trial identified that up to 22% of AML patients have the extramedullary form[3]. Extramedullary AML patients have no clinically approved treatments and limited experimental treatment options, with many clinical trials explicitly excluding this difficult to treat form of AML.

Myelodysplastic Syndromes (MDS)

MDS are a group of blood cancers that affect the production of normal blood cells in the bone marrow. These include chronic myelomonocytic leukaemia (CMML), , atypical chronic myeloid leukaemia (aCML) and myelodysplastic/ myeloproliferative neoplasms unclassifiable (MDS/MPN)[4].

MDS has a very high risk (1 in 3) of the patient progressing to AML and high risk MDS is an earlier stage of AML. There are more than 10,000 patients diagnosed with MDS each year in the USA, which is approximately half the rate of AML.

Clinical Trial Design

This open label Phase 1 trial with a Phase 2 dose expansion phase will recruit up to 60 patients with ^{18}F-FDG PET/CT imaging-identified extramedullary AML at 10 clinical sites using a two-stratum (arm) design. The first stratum will utilise Zantrene as a high dose, single agent treatment over 7 days in patients with extramedullary AML who are able to tolerate high intensity chemotherapy, followed by one or more cycles of consolidation treatment of Zantrene in combination with Ara-C, a standard of care drug.

The second stratum will use Zantrene as a low dose FTO-targeted agent in combination with the oral hypomethylating agent, ASTX727 for MDS or AML patients unwilling, or unable to tolerate high intensity chemotherapy. Published preclinical data from City of Hope Hospital / Beckman Research Institute, by Professor Chen's Laboratory identified that FTO inhibition synergized with decitabine in leukaemic cells[2]. Subsequent preclinical work by Race in collaboration with the Verrill's Laboratory validated these findings in the EMD setting. Using a mouse model of EMD AML, A/Prof Verrills demonstrated that optimal dosing of decitabine and Zantrene is able to synergistically target extramedullary AML tumours as well as AML lesions in the bone marrow and spleen (ASX Announcement: 17 March 2022).

The trial primary endpoint will be complete response (CR) and complete response with incomplete haematological recovery (CRi), with the clinical aim of bridging the patient to an allogeneic hematopoietic stem cell transplant (Stratum 1), and safety and tolerability of the decitabine/Zantrene regimen (Stratum 2). Key secondary endpoints include safety and tolerability of Zantrene, overall and event-free survival, and the correlation of FTO expression or other biomarkers with response to treatment.

Full details of the trial will be published on www.clinicaltrials.gov once RGO approval has been received.

Indicative Timelines and Reporting

The trial is expected to take 36 to 40 months to complete with full patient recruitment over approximately 18 months.

This trial is open label in nature, so patient outcome results are obtained as patients are treated. We intend to announce progress updates on a regular basis, but not at the individual patient level. The first patient is expected to begin treatment soon after governance approval is obtained.

Race CMO Dr David Fuller said *"We are pleased to receive this first human ethics approval and expect to expand the study to more approved Australian sites in the coming months. In addition, based on positive feedback from European clinical key opinion leaders and supported by the proceeds of our recent share purchase plan, we look forward to adding additional trial sites in Europe."*

Clinical Trial Summary

Study Title	An Open-label Two Strata Study of High Dose Bisantrene in Combination with Cytarabine Arabinoside (Ara-C) or Low Dose Bisantrene in Combination with Oral Decitabine/Cedazuridine for the Treatment of Acute Myeloid Leukemia Patients with Extramedullary Disease. BISECT (*BI*Santrene *E*xtramedullary *C*hemo*T*herapy)
Phase of Development	Phase 1b with Phase 2 dose expansion
Active Ingredient	bisantrene dihydrochloride (Zantrene)
Study Description	A two-stratum trial of Zantrene in patients with extramedullary AML or MDS and CMML diagnosed by ^{18}F-FDG PET/CT imaging.
Principle Investigator	A/Prof Anoop Enjeti
Sponsor	Race Oncology
Indication/population	Adult men and women ≥18 years of age with AML or MDS presenting with non-CNS extramedullary disease.
Number of Subjects	**Stratum 1:** up to 30 patients **Stratum 2:** up to 10 patients (dose escalation stage); up to additional 20 patients in the expansion stage
Study Period	36 – 40 months
Study Design	A two strata open-label non-randomized study of high dose bisantrene treatment given as a monotherapy induction and in combination with Ara-C as consolidation (Stratum 1) and lower dose bisantrene in combination with oral decitabine/cedazuridine (ASTX727) (Stratum 2) in patients with extramedullary AML, or high risk MDS and CMML. As the patient population is considered without existing treatment options, a comparator arm will not be used.
Statistical methods	Bayesian Optimal Interval (BOIN) model-based design based on observed response rate of 30% for RR AML where the true response rate is expected to be <20% applying a 90% power.
End Points	**Primary (Stratum 1):** Achievement of a complete response (CR) or complete response with incomplete count recovery (CRi). **Primary (Stratum 2):** Tolerability and safety. **Key Secondary:** Achievement of a PET/radiologic overall response, i.e. complete or partial metabolic response, after cycles 1, 2 and 4 (Stratum 1) and after cycles 4,6,9 and 12 (Stratum 2). **Other Secondary:** number of patients bridged to transplant and time to transplant (Stratum 1), pharmacokinetics, FTO and other biomarker status, event free survival, overall survival
Participating Centres	10 sites

Q&A

What is ASTX727 and why was it chosen for the trial?

ASTXZ727 (trademark INQOVI®) is an oral formulation of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor and has been approved by the FDA for treatment of adult patients with MDS. It is currently in late-stage clinical trials for AML patients.

Will this trial support orphan drug registration of Zantrene under the FDA 505(b)(2) pathway?

The Stratum 1 patients will be treated as per the historical Zantrene AML trials (i.e. 250 mg/m^2/day over 7 days). This trial will build on the modern and historical data for a potential 505(b)(2) approval

Stratum 2 may provide clinical evidence for the use of Zantrene/decitabine combination in patients unwilling or unable to tolerate high intensity chemotherapy.

Does this trial target FTO in AML & MDS patients?

Yes. This trial builds on the preclinical studies of our advisor Professor Jianjun Chen of the City of Hope Hospital. His team discovered in AML cells that inhibition of FTO synergises with the hypomethylating standard of care drug, decitabine. This combination will be clinically explored in patients unable or unwilling to tolerate high intensity chemotherapy (Stratum 2). This synergy has been confirmed in both cell cultures and animal models of EMD AML by Associate Professor Nikki Verrills of the University of Newcastle (ASX Announcement: 17 March 2022).

Why was the trial split into two stratums?

There is currently no standard of care treatment for the extramedullary form of AML or MDS. As many AML patients are unable or unwilling to tolerate high intensity chemotherapy, we wanted to ensure we could offer a treatment option for all patients enrolled in the trial. In addition, success with the low intensity FTO-targeted regime could potentially be an attractive alternative for healthier patients unwilling or unable to undertake intense chemotherapy.

When can shareholders expect progress updates on the trial?

This trial is open label in nature, so patient outcome results are obtained as patients are treated. We intend to announce progress updates on a regular basis, but not at the individual patient level. The first patient is expected to begin treatment soon after governance approval is obtained.

References

1. Prof Chen recently joined Race's Scientific Advisory Board (ASX Announcements: 16 April 2021).

2. Su, R. *et al.* (2018). R-2HG Exhibits Anti-tumor Activity by Targeting FTO/m6A/MYC/CEBPA Signaling. *Cell* 172, 90-105.e23.

3. Stölzel, F., Lüer, T., Löck, S., Parmentier, S., Kuithan, F., Kramer, M., et al. (2020). The prevalence of extramedullary acute myeloid leukemia detected by 18FDG-PET/CT: final results from the prospective PETAML trial. *Haematologica*, *105*(6), 1552–1558.

4. www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/myelodysplastic-syndromes/

-ENDS-

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 breast cancer. Race is evaluating this discovery.

The Company also has compelling clinical data for Zantrene as a chemotherapeutic agent and is in clinical trial 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

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