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ASX Announcement

Impressive 40% clinical response rate in Phase II Bisantrene AML Trial

- **Analysis of Phase II trial of Bisantrene for relapsed or refractory Acute Myeloid Leukaemia showed an objective clinical response in 40% of patients**
- **Of the 10 patients treated, one patient achieved a complete remission and three patients achieved partial remission, a response rate comparable to historical bisantrene trials**
- **Bisantrene had marked activity in 4 out of 4 patients with the difficult to treat extramedullary (outside of the bone marrow) form of AML**
- **Bisantrene was well tolerated with no unexpected serious toxicities**
- **R/R AML represents a significant therapeutic challenge with no clearly established standard of care**

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16 June 2020 – Race Oncology Limited (ASX:RAC) is pleased to report positive clinical data from the investigator initiated Phase II clinical trial of bisantrene, conducted at Israel's Sheba Medical Centre. This open label, single agent trial studied patients (n=10) with relapsed or refractory Acute Myeloid Leukaemia (R/R AML) who on average had failed three prior lines of treatment. Bisantrene was found to be well tolerated, and after only a single course of treatment, had an overall clinical response rate of 40%.

Professor Borje Andersson, Chair of Race's Clinical Advisory Board and an international authority in clinical leukaemia and stem cell research commented, "While bisantrene had been demonstrated to be an effective AML salvage drug in the 1980's, the data we had were old. It was important for us to study it by today's standards using the current formulation, as we sought to confirm whether our strategy of repurposing this drug was sound. We also wanted to confirm that bisantrene could still generate a meaningful response rate in this highly frail patient population with heavily pre-treated AML."

"Importantly, in this study we saw a meaningful reduction in leukaemic disease burden and an overall response rate in 40% of the patients. While we must study the drug further, it appears that with this kind of response, bisantrene based therapy may have potential to serve as an important bridge to an allogeneic stem cell transplantation in patients who otherwise have few therapeutic options."

Background

R/R AML remains a significant therapeutic challenge[1]. While meaningful therapeutic gains have been achieved in recent years with the introduction of new targeted drugs, clinical outcomes still remain unsatisfactory[2].

The class of drugs referred to as anthracyclines are an essential component of induction chemotherapy for AML patients, however mainly due to cardiotoxicity concerns, they are not broadly

prescribed in relapsed or refractory AML settings. Bisantrene, which is an anthracene with anthracycline-like activity, was shown in earlier studies to be an effective salvage therapy in R/R AML with little or no discernible cardiotoxicity.

In this study, Israel's Chaim Sheba Medical Centre studied the clinical efficacy of bisantrene in a cohort of heavily pre-treated, R/R AML patients under the leadership of Principal Investigator, Professor Arnon Nagler.

This investigator initiated study consisted of 10 patients who had received a median of three lines of prior therapy, including 7 patients who had relapsed following allogeneic stem cell transplantation. Three patients had an antecedent myeloid disorder while four patients had extramedullary disease (located outside of the bone marrow) at the time of recruitment.

Of the ten patients, one achieved a complete remission (CR) and three patients achieved a partial remission (PR), resulting in an overall response rate of 40% after only a single course of bisantrene treatment, with one patient being bridged to allogeneic stem cell transplantation. No patients were removed from the study during treatment.

Next generation DNA sequencing of the responding patient samples identified a wide array of genetic mutations including those associated with activated signalling, splicing, chromatin modification, and epigenetic modification. Bisantrene had marked activity in patients with the difficult to treat extramedullary AML, such as leukemia cutis, chloromas, and CNS disease[3]. Interestingly, all four patients who had a clinically significant response to bisantrene had extramedullary disease.

The most frequently reported serious adverse event were thrombocytopaenia (low blood platelets) (60% Grade 3/4) and mucositis (mouth ulcers) (60% Grade 3/4), both of which are expected side effects of anthracyline and anthracene chemotherapeutics. One patient experienced transient Grade 1 kidney toxicity and there were no liver toxicities observed. These adverse events are at similar or lower levels to those seen in the historical bisantrene trials[4]. Importantly, no anaphylactoid-type reactions were observed in any patient over the course of treatment, a serious adverse event regularly observed in the historical trials.

Chief Scientific Officer, Dr Daniel Tillett said, "A key focus of this trial was a determination of bisantrene's safety in a modern context, so it was encouraging to see the drug's tolerability profile compared favourably with other commonly used chemotherapy agents such as the anthracyclines. The side effects were in keeping with what we would expect to see with all chemotherapeutics of this class and provide further evidence of bisantrene's clinical safety.

"These results are pleasing from both a safety and activity perspective, particularly given the clinically challenging patient population included in this trial."

The Sheba investigators concluded that the study showed bisantrene to be an agent with an acceptable safety profile and promising anti-leukemic activity.

Data from this study will be submitted by the Sheba team to a peer-reviewed medical journal for publication.

1. Schlenk, R. F., Jaramillo, S., & Müller-Tidow, C. (2018). Improving consolidation therapy in acute myeloid leukemia - a tough nut to crack. *Haematologica*, *103*(10), 1579–1581.

2. Estey, E., Levine, R. L., & Löwenberg, B. (2015). Current challenges in clinical development of "targeted therapies": the case of acute myeloid leukemia. *Blood*, *125*(16), 2461–2466.

3. Solh M, Solomon S, Morris L, Holland K, Bashey A. Extramedullary acute myelogenous leukemia. Blood Rev. 2016;30(5):333-339. doi:10.1016/j.blre.2016.04.001

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4. Rothman, J. (2017). The Rediscovery of Bisantrene: A Review of the Literature. *Int J Cancer Res Ther*, *2*(2), 1–10.

Next steps

Executive Chairman of Race Oncology, Dr John Cullity commented, "This drug is talking to us. As this was an open label, single agent trial, we can be confident that it was the bisantrene exposure which generated the positive results."

"The patient cohort had advanced AML and had previously failed an average of three lines of therapy, so they were always going to be tough to treat. A 40% overall response rate after only a single course of treatment markedly exceeds expectations. It's a hugely promising result and one which reinforces our development plans for bisantrene."

In line with the Company's '5-Path' clinical development strategy (ASX announcement 14 Nov 2019), a follow-up study combining bisantrene with other anti-leukemic drugs is currently in advanced planning.

Investor briefing

A group investor briefing will be held to discuss the significance of the trial results in more detail **on Wednesday 17 June 2020 at 10:30am Australian Eastern Time** (8:30am Western Australian/Hong Kong time; 8:30pm New York time and 5:30pm San Francisco time on Tuesday 16 June 2020).

Participants will need to pre-register for the call, using the following link:

https://us02web.zoom.us/webinar/register/WN_UZqeygRqSwq41YoH3PBWEw

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About Race Oncology (RAC: ASX)

Race Oncology (RAC) is a drug development biotech with a Phase II/III cancer drug called Bisantrene. RAC has compelling clinical data for Bisantrene in acute myeloid leukaemia (AML) as well as breast and ovarian cancer. RAC is pursuing an exciting '5-Path' clinical development strategy that involves parallel US and Australian clinical trials in AML, breast and ovarian with clinical trials to begin in 2020.

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Clinical trial summary

Study title	Bisantrene for relapsed/refractory AML
Phase of development	Phase II
Investigational product	Bisantrene
Conditions	Relapsed or refractory Acute Myelogenous Leukaemia (AML)
Registration	NCT03820908
Study description	The Phase II trial, aims to generate clinical remissions (CR) in patients with AML, who are resistant to other therapy (refractory), have relapsed after previous therapy, or cannot receive further anthracycline treatment.
Masking	None (open label)
Number of subjects	The trial was expected to recruit 12 adult subjects over 12 months. 10 subjects were recruited.
Study design	This was a Phase II open-label single arm single center study of bisantrene in the treatment of adult R/R AML. Ten patients were recruited at the Chaim Sheba Medical Center between July 18, 2019, and February 3, 2020 under approval by an Institutional Review Board in accordance with the Declaration of Helsinki (5792-18 CMC). All patients provided written informed consent before administration of any study treatment. Bisantrene (250 mg/m^2 once daily for 7 days) was administered via an intravenous infusion over 2 hours on days 1-7. Supportive care included administration of filgrastim (5 mcg/kg) at day +1 from completion of therapy, antifungal prophylaxis with fluconazole (400 mg QD from day +1), and trimethoprim-sulfamethoxazole (QD upon blood count recovery). Patient therapy was limited to one completed cycle of bisantrene.
Patient population	Patients with AML, who are resistant to other therapy (refractory), have relapsed after previous therapy, or cannot receive further anthracycline treatment.
Endpoints	Overall survival (timeframe: 24 months): • Overall survival was calculated from the day of bisantrene administration until death or last follow-up. Leukaemia-free survival (timeframe: 24 months): • Leukaemia-free survival will be calculated from the day of bisantrene administration until relapse, death of any cause, or last follow-up.
Participating centres	Chaim Sheba Medical Center, Ramat Gan, Israel
Principal Investigator	Professor Arnon Nagler
Start date	25 July 2019
End of recruitment	18 March 2020

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Q&A

Given bisantrene has been in used in many trials in the past, why did you decide to support this investigator initiated trial?

Before embarking on large scale clinical trials of bisantrene, it was important to confirm that the historical data could be reproduced in today's patients with our manufactured bisantrene. AML patients are treated very differently than patients were 30 to 40 years ago, and in particular, AML patients now have many more treatment options. It was possible that while bisantrene once worked well in AML, it may no longer work in much more heavily pre-treated patients. This trial showed that bisantrene is still a safe and effective treatment in the 21st century clinical environment.

What is the clinical significance of this data? How should investors interpret these results?

The two major takeaways from this trial are:

1. Bisantrene works, even in patients that are very difficult to treat and resistant to all other treatment options.

2. Bisantrene is safe, with only the side effects seen that are expected for this class of drug.

The results are unambiguously positive for the potential of bisantrene.

Are the results statistically significant?

The number of ten patients treated makes it impossible to talk about statistical significance in any meaningful way for any of the results. However, historical experience tells us that in a heavily pretreated AML patient population you are lucky if you can get a 20-30% response rate with any salvage treatment, and the historical trials with bisantrene in acute leukemia yielded response rates of anywhere from about 20-50%, so the current data are certainly within that same range, which testifies to the efficacy of the new formulation.

Future company sponsored trials of bisantrene will include a greater number of patients than in this trial.

How does the data compare with bisantrene's performance in historic clinical trials?

The historical clinical response rate in R/R AML was in the range of 20% to 50%[1]. These historical trials included patients that experienced far fewer treatment cycles, with the majority having only one prior treatment before receiving bisantrene. The patients in this trial were much more heavily treated (average of three prior therapeutic courses) and so were expected to be far less likely to respond. Beyond the inclusion of an inline 0.22µm filter to prevent particle infusion, the treatment protocol followed in this trial was identical to the historical AML trials.

Our expectation at the beginning of this trial was that a 10% response rate would be a very positive and result and that it was quite likely that no patients would respond. The results of this trial far exceeded our expectations.

How many of the patients treated are still alive?

The trial is still ongoing and the primary objectives of this trial (overall survival and leukemia-free survival) will be assessed 24 months from treatment initiation. It is our expectation based on the patient cohort (late stage and heavily pre-treated) that long term survival of these patients is unlikely.

What is an 'investigator initiated' trial? What did this mean for this trial?

Investigator initiated clinical trials are where the investigator (like Sheba) largely designs, runs and pays for trial costs. (In the case of this trial, Race provided a financial grant to Sheba to contribute to trial costs.) This is in contrast to company sponsored trials, where a corporate entity (like Race) has responsibility for trial design and cost.

Why was only one cycle of bisantrene given in those patients that showed a complete response?

The study was designed such that patients received only one course of bisantrene unless there was a CR, in which case a consolidation course at the same daily level of 250mg/m2 was allowed daily for three days. The patient in this trial who achieved a CR went onto receive allogeneic stem cell transplant in place of that consolidation course. This was the best treatment option for the patient which matched up with a stem cell donor being available. This approach provided the best chance of longer term remission.

How does a 40% clinical response rate compare with other AML cancer drugs?

As stated above, the 40% is at least within the expected range for any successful phase II study in this kind of patient population. We would actually have considered already 10% to be a promising trial result.

Bisantrene is a non-targeted agent that worked across a wide range of genetic backgrounds and high risk mutations. Unlike the new targeted drugs that are limited to a small sub-population of AML patients, bisantrene offers the potential to be used in most/all R/R AML patients.

The trial was supposed to recruit 12 patients, but only 10 were treated. Why?

The goal of this trial was to confirm the historical safety data could be reproduced before we embark on modern combination trials that are likely to yield deeper and more long-lasting remissions. Given the COVID-19 situation in Israel and the likely delay this would have caused, recruitment of the final two patients, we agreed with the investigators to end the trial early. Continuing the trial would not have added significantly to the results and would have only delayed the start of our next study of bisantrene in combination with other AML drugs.

What are the next steps for bisantrene in AML?

Race has three planned paths focused on AML in its 5-path strategy for bisantrene: Path 1. Combination treatment in paediatric R/R AML; Path 2. Combination treatment in adult R/R AML; and Path 3. MRD(+) AML. Race is in advanced planning of all three trials.

What are the plans for publication of these trial results?

The final report was supplied as manuscript which will be submitted shortly for publication in a cancer journal. The principal investigator also intends to submit the data for presentation at a major international haematology conference to be held in USA later in the year. Race will update the market when both of these activities occur.

Will this trial generate partnering interest from 'big pharma' for bisantrene?

This is a difficult question to answer at this point in time, but our experience suggests that bisantrene fits the profile of drugs that 'big pharma' are interested in licensing. Race intends to pursue all opportunities to partner that provide a positive return to our shareholders.

1. Rothman, J. (2017). The Rediscovery of Bisantrene: A Review of the Literature. *Int J Cancer Res Ther*, *2*(2), 1–10.

2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation

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Glossary

CR (Complete Remission)

Less than 5% blast (cancer) cells in the bone marrow and a full recovery of the bone marrow maturation and peripheral blood counts, an absolute neutrophil count of more than 1,500/µl and at least 100,000 platelets per µl. No extramedullary disease.

CRi (Complete Remission with Incomplete Hematologic Recovery)

Less than 5% blast cells in the bone marrow and complete recovery of bone marrow maturation, but not recovery of neutraphils or platelets to the level needed for CR. No extramedullary disease.

PR (Partial Remission)

Major reduction in blast cells (5%-25% blast in bone marrow) with recovery of bone marrow maturation and some recovery of peripheral blood counts. If extramedullary disease, there is a reduction to more than 50% of such disease.

Extramedullary AML

Presences of cancer outside the bone marrow. Can occur in any organ, often in the skin and brain.

Antecedent Myeloid Disorder

Antecedent Myleoid Disorder is an AML that occurs after more than three months of documented preceding haematological disorder, such as unclear anaemia or a pre-leukaemic syndrome. Often very aggressive and refractory to current cancer treatments.

Investigator Initiated Clinical Trial

A clinical trial designed and supervised by an academic or hospital based clinician.

Company Sponsored Clinical Trial

A clinical trial designed and sponsored (paid) by a biotechnology or pharmaceutical company.

High Risk AML Mutations

Changes to the DNA of the AML cells that make the cancer aggressive and/or hard to treat. Patients with high risk AML mutations often have a short life expectancy and few treatment options.

'Big Pharma'

Large international pharmaceutical companies. These companies regularly partner with small biotech companies to fund the clinical development of new pharmaceuticals.

Anthracycline

A family of chemotherapeutic drugs that cause DNA damage. While they are more toxic to cancer cells than normal cells, they do damage many normal cells causing serious short and long term serious side effects. The anthracyclines are well known for having a cumulative toxic effect on the heart which limits their use in cancer medicine.

Chemotherapeutic drug

A toxic drug that is used to treat cancer. The drugs are more toxic to cancer cells than normal cells, but can cause serious side effects in patients.

Allogeneic stem cell transplantation

A treatment for leukemias where the bone marrow from a healthy donor is given to the patient. An important treatment for patients with AML as it can result in long term survival or cure.

Salvage Drug

A drug given to a cancer patient who has relapsed or not responded to standard cancer treatments.

Open label

A clinical trial where both the patient and treatment doctor know what treatment they are receiving. Often used where it would be unethical to give a patient a placebo and/or where the treatment can not be hidden from the patient as the effects of treatment are obvious to the patient.

AML (Acute Myeloid Leukaemia)

A type of leukaemia (blood cancer), often aggressive and hard to treat.

Refractory AML

An AML cancer type that does not respond to current cancer treatments.

Relapsed AML

AML that returns after a complete remission.

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