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ASX Announcement

Impressive Bisantrene Phase 2 AML Trial Data to be Presented at the 65th American Society of Hematology Annual Conference

- Bisantrene in combination with fludarabine and clofarabine administered over four days induced a clinical response in 6 of 15 evaluable patients (40%) with advanced relapsed or refractory Acute Myeloid Leukaemia, with five patients receiving a potentially curative stem cell transplant
- The bisantrene combination was found to be safe and well tolerated without clinically relevant cardiotoxicity or tumour lysis syndrome
- The trial abstract has been peer-reviewed and the interim results selected for presentation at the prestigious American Society of Hematology 65th Annual Conference, 9-12 December 2023.

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6 November 2023 – Race Oncology Limited ("Race") is pleased to announce interim clinical results from an ongoing investigator-initiated Phase 2 trial of bisantrene in combination with fludarabine and clofarabine in relapsed or refractory Acute Myeloid Leukaemia (R/R AML) patients. The trial is running at the Sheba Medical Centre, Israel, under the supervision of key opinion leader Professor Arnon Nagler. Results of this trial have been chosen by the conference committee for presentation at the prestigious American Society of Hematology (ASH) 65th Annual Conference being held on the 9-12 December 2023.

The oral poster presentation entitled *"Bisantrene in combination with Fludarabine and Clofarabine as Salvage Therapy for Adult Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) – An Open-label, Phase II Study"* describes clinical results from the first 15 evaluable patients treated on study since August 2021 (NCT04989335). The presentation abstract was released from embargo by ASH on 2 November 2023.[1]

Highly Positive Interim Results

Six of the 15 evaluable patients (40%) responded to Bis/Clo/Flu treatment (five complete responses, one partial response), with three of the clinical responders having active extramedullary disease (EMD). Five of the six treatment-responsive patients were able to be bridged to a stem cell transplant (SCT) within one to three months of treatment. Of the five stem cell transplanted patients, three have since died; one from graft-versus-host disease, one who relapsed within four months of transplant, and one of infection after two years. The two other patients remain disease free and in complete remission.

Professor Dr Anoop Enjeti, Director of Haematology at the Calvary Mater Newcastle and John Hunter Hospitals commented: *"This clinical trial of bisantrene in combination with intensive chemotherapy produced very encouraging results in younger AML patients with advanced relapsed, refractory and resistant acute myeloid leukaemia (AML). Many of these patients achieved a complete or a partial remission, enabling a significant proportion to go on to a bone marrow transplant. These impressive results provide proof of concept supporting further trials of bisantrene in combination with other AML treatments to improve outcomes for this leukaemia."*

Prof. Enjeti is an independent specialist in haematological cancers including AML and was not involved with the Sheba study. He is a highly experienced clinical haematologist, having designed and led more

than 25 clinical trials and is the co-chair of the MDS/AML working party for the Australasian Lymphoma and Leukemia Group (ALLG) for Cooperative Clinical Trials.

Executive Director, Dr Pete Smith commented: *"These are highly positive outcomes in a heavily pre-treated patient population. We await with interest the release of the poster at ASH in December. To see such meaningful clinical responses in a group that would typically be receiving palliative care is striking. It is also encouraging that the safety profile was manageable, even for this advanced patient population."*

Patient Population

The median patient age was 48 years (range 19-69) and the median number of prior lines of therapy was four (range 3-9). All patients were refractory to prior regimens, which included cytarabine/daunorubicin; fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida), venetoclax; azacitidine; gilteritinib, radiation therapy, and CAR-CD19 for 8:21 (genotype) AML.

Due to the expected low probability of achieving a clinical response in this treatment resistant patient population, the primary endpoint for the study was 'any clinical response' (partial response, complete response, or complete response with incomplete blood count recovery). The secondary endpoint was 'any clinical response that enabled a stem cell transplant'. Safety and cardiac monitoring data were captured as exploratory endpoints.

Five patients died from disease progression or bacterial/fungal infection before they could be evaluated for a clinical response to treatment. This was not an unexpected outcome given the advanced disease state of this heavily pre-treated salvage AML patient population. A recent retrospective analysis at the MD Anderson Cancer Center of 1258 salvage AML patients who had received a median of less than two lines of salvage treatment, found the early mortality rate to be almost one in five patients (18%) during salvage therapy.[2]

Treatment side-effects

The most common side-effect was treatment-related neutropenic fever, observed in 18 patients. Ten patients developed transient liver toxicity (Grade 1-3) that resolved in all patients with conservative therapy. Transient liver toxicity is a well-known toxicity of clofarabine, where rates of up to 60% have been observed in multiple clofarabine-containing treatment regimens.[3,4] Four patients had Grade I (mild) renal toxicity and seven had mild fluid retention.

Importantly, clinically relevant cardiotoxicity was not observed in any patients. Clofarabine has been associated with rates of heart left ventricular systolic dysfunction of up to 27% in clofarabine-containing treatment regimens.[5]

Conclusion

Professor Nagler, the study Principal Investigator, concludes in the abstract: *"These rather impressive results in such a heavily pre-treated population support further studies of bisantrene-based combinations, including those with venetoclax or hypomethylating agents."*[1]

Study Details

Refractory or relapsed Acute Myeloid Leukemia

Primary refractory or relapsed AML (R/R AML) is associated with poor prognosis and remains a serious therapeutic challenge. Primary refractory AML is defined by the absence of a complete response (CR), manifested by a blast count of ≥5% in bone marrow after one or two cycles of intense induction chemotherapy.

Even when CR is achieved through intense chemotherapy, approximately half of the younger and 80% of older patients, relapse. In both clinical situations, refractory or relapsed AML, active disease remains a major therapeutic challenge despite recent advances. This challenge is especially acute in patients who have failed four or more lines of treatment and where clinical responses to new treatments are rare.

Clinical Trial Design

The trial is an open-label, Phase 1b/2 study of intravenous Bis/Clo/Flu (bisantrene, clofarabine, fludarabine) in cohorts of up to 12 adult patients with R/R AML. It involves a Phase 1b dose escalation stage to establish the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of the combined Bis/Clo/Flu regimen, followed by a Phase 2 expansion stage to determine efficacy and confirm the safety of Bis/Clo/Flu at the RP2D in up to 17 patients.

Phase 1b, Dose-Escalation (Lead-in Stage)

The trial uses a two-cohort dose escalation schema of a standard 3 + 3 design. Cohort 1 enrols three patients to receive the Bis/Clo/Flu regimen for four consecutive days. If no dose limiting toxicities (DLTs) occur in the first three patients by day 30 of their first cycle of treatment, then Cohort 2 receives treatment for five days, with the extra day representing a dose escalation.

Phase 2, Expansion (Efficacy Stage)

Up to 17 patients can be enrolled into a Phase 2 expansion efficacy cohort using a Simon 2-stage design. Initially, 9 patients are enrolled and treated at the R2PD of Bis/Clo/Flu, as determined in the Phase 1b part of the study. If no patient responses are observed in the first 9 subjects according to the response criteria outlined in the European Leukemia Net (ELN) guidelines, the study is terminated for futility. If at least one patient shows a response, eight more patients are enrolled and treated. If three or more of the patients treated in Stage 2 respond, the null hypothesis of treatment futility is rejected.

Efficacy assessments are based on bone marrow examination at a minimum of two time points on Day 21 and 30. A further bone marrow examination may be performed on Day 42 at the investigator's discretion, based on patient's disease and performance status and/or peripheral blood hematology results during the treatment course and between Days 21 to 42.

Treatment is terminated upon any sign of progressive/recurrent disease and/or referral to pre-transplant conditioning therapy for (allogeneic) stem cell transplantation. Patients who do not progress or experience any DLTs may receive a second course of treatment for the same duration as in their first cycle. All patients are followed-up for disease free survival (DFS) and overall survival (OS) every three months for a further 12 months following completion of treatment.

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Q & A

Is this a good result?

Yes. This is an outstanding result considering the treatment history of the patients in this trial to date. Many clinicians would consider even a single patient being able to be bridged to a stem cell transplant a success in such a heavily pre-treated salvage population. It is difficult to find published trial results for a comparable patient population who have failed this number of lines of therapy since many trials exclude such treatment-advanced patients. This is because in the opinion of many clinicians, a patient's chance of responding to any new treatment is too low to outweigh the risks associated with further treatment.

What was the outlook for the patients in this trial without treatment?

Dire. Advanced AML salvage patients have a life expectancy measured in weeks if they do not receive efficacious treatment.

How difficult was it to effectively treat the AML patients in this trial?

Very challenging. The patients in the trial to date had failed a median of four lines of prior treatment, with some patients failing nine lines before entering the trial. In many locations (*e.g.,* Australia), AML patients who fail this many lines of prior treatment are likely to be only offered palliative (supportive) care as clinicians believe that the risks of using more experimental treatments exceed the chance of the patient responding. For example, an efficacious AML treatment that might work in 70% of patients as a first-line therapy may only work in 5% of patients who receive it as a fifth-line therapy. There are many reasons for the poor treatment response rate with increasing lines of therapy, including a decline in patient health as the disease progresses, mutations that arise during treatment that make the cancer multi-drug resistant, and enrichment for patients with most aggressive and non-responsive cancers as the responsive cancers have already been treated effectively at earlier lines of therapy.

How do the results compare to the earlier Phase 2 trial completed at Sheba?

The clinical response rate in the earlier trial of 10 patients treated at Sheba with bisantrene over seven days was also 40% (ASX announcement: 16 June 2020). It is not appropriate to compare the two studies since the patients in the first trial were less heavily pre-treated than in the current ongoing trial.

Were there any EMD AML patients in this trial to date? How did they respond?

Yes. There were five patients with active EMD disease in this trial and three responded to treatment.

Does this data help move bisantrene into less advanced AML patients that are more likely to respond to treatment?

Yes. All new oncology drugs and drug combinations start out in the hardest to treat patients with the most advanced disease. As clinical understanding grows around a drug's efficacy and side-effects, clinicians will start to use the drug in earlier-stage patients who are more likely to respond to treatment.

When will the full data be released?

The oral poster will be presented at the ASH meeting between 9-12 December 2023. The trial is still recruiting, but as with the first Phase 2 trial of bisantrene run at Sheba[6], we expect a peer-reviewed journal article will be published once the trial finishes.

Will the poster contain any m^{6}A RNA or FTO results?

This is unknown, although we note that Dr Dan Dominissini, a leading global expert on m^{6}A RNA biology, is an author on the poster presentation.

What are the commercial implications of these results for Race?

Positive clinical trial data is the foundation of commercialisation or partnership discussions with large pharmaceutical companies. Race continues to engage with potential pharma partners and will update the market on progress when appropriate.

What plans does Race have for future AML clinical trials of bisantrene?

Race is considering a range of clinical options for the use of bisantrene in the AML setting and is in advanced discussions with clinicians in Australia and internationally. Race will update investors once these discussions have been finalised.

References

1. https://ash.confex.com/ash/2023/webprogram/Paper178286.html

2. Sasaki, K. *et al.* Early Mortality as a Quality Indicator in Frontline and Salvage Acute Myeloid Leukemia. *Clin. Lymphoma Myeloma Leuk.* (2023) doi:10.1016/j.clml.2023.08.016.

3. Gill, H. *et al.* Clofarabine, cytarabine, and mitoxantrone in refractory/relapsed acute myeloid leukemia: High response rates and effective bridge to allogeneic hematopoietic stem cell transplantation. *Cancer Med* **9**, 3371–3382 (2020).

4. Kaya, A. H. *et al.* Efficacy of CLARA in recurrent/refractory acute myeloid leukaemia patients unresponsive to FLAG chemotherapy. *J. Chemother.* **30**, 44–48 (2018).

5. Kamphuis, J. A. M. *et al.* Cancer Therapy-Related Cardiac Dysfunction of Nonanthracycline Chemotherapeutics What Is the Evidence? *JACC: CardioOncology* **1**, 280–290 (2019).

6. Canaani, J. *et al.* A phase II study of bisantrene in patients with relapsed/refractory acute myeloid leukemia. *Eur J Haematol* **106**, 260–266 (2021).

About Race Oncology (ASX: RAC)

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

Race's lead asset, bisantrene, is a small molecule anthracene chemotherapeutic. Bisantrene has a unique and rich clinical history with demonstrated therapeutic benefits in both adult and paediatric patients, a well characterised safety profile, and compelling clinical data demonstrating an anti-cancer effect and less cardiotoxicity than other comparable agents.

Race is developing bisantrene to address the high unmet need of patients across multiple oncology indications, with an initial focus on metastatic breast cancer (lead indication) and acute myeloid leukaemia (AML) exploring anti-cancer plus cardio-protection in synergy with known standards of care.

As part of its clinical and preclinical programs, Race is investigating the effect of bisantrene on the m^6A RNA pathway, following independent research by the City of Hope identifying bisantrene as a potent inhibitor of FTO (Fat mass and obesity-associated protein). Dysregulation of the m^6A RNA pathway has been described in numerous peer reviewed studies to be a driver of a diverse range of cancers.

Race Oncology is in collaboration with City of Hope, MD Anderson, Sheba City of Health and UNC School of Medicine, and is actively exploring partnerships, licence agreements or a commercial merger and acquisition to accelerate access to bisantrene 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 https://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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