ASX Announcement

Zantrene AML Trial at Chaim Sheba, Israel Advances to Phase 2

- **Phase 1b dose escalation stage of the Phase 1b/2 Zantrene study in AML has completed using a 4-day treatment of Zantrene in combination with fludarabine and clofarabine**
- **Encouraging clinical responses were observed in this very heavily pre-treated AML patient population with 3 of the 6 patients bridged to a stem cell transplant**
- **The study led by Professor Arnon Nagler of the Chaim Sheba Medical Center, Israel will now advance to the Phase 2 efficacy stage recruiting up to 17 patients.**

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27 May 2022 – Race Oncology Limited ("Race") is pleased to announce the dose escalation Phase 1b stage of the relapsed or refractory Acute Myeloid Leukaemia (R/R AML) trial running at the Chaim Sheba Medical Centre, Israel has successfully completed after the treatment of the first six patients.

The six patients were heavily pre-treated and had received a median of four prior lines of AML treatment (range 2-8).

By design, the primary endpoint of the initial phase of this 2-stage clinical trial is establishing the recommended dose to be used in the subsequent Phase 2 expansion (efficacy) stage. This first stage requires identifying the treatment dose level that achieves two or fewer dose-limiting toxicities (DLTs) from six consecutively treated patients. In the initial six patients treated, two DLTs were reported (one Grade 3 elevated liver enzymes and one Grade 5 infection). Both DLTs occurred in the most heavily pre-treated patients who had received five and eight prior lines of treatment, respectively.

Efficacy results in this refractory patient population were very encouraging, with one patient showing a complete response (CR) based on morphology, two patients having a partial response (PR) including one with extramedullary disease, two showing no response (NR), and one patient not assessable (NA) due to death from infection. Infection is a known side effect of all intensive chemotherapeutic regimens and is one of the leading causes of death in AML patients[1].

Three patients (1 CR and 2 PR) were bridged to an allogeneic stem cell transplant. Bridging a patient to transplant is an important positive outcome in AML treatment as it offers the patient the potential of long-term remission. Of note, these three patients had all received less than five prior lines of treatment. Poor or no response to known efficacious treatments is common and expected in heavily pre-treated cancer patients[2].

The trial will now progress to the Phase 2 efficacy (expansion) stage using a 4-day schedule of Zantrene® (bisantrene dihydrochloride) in combination with fludarabine and clofarabine.

Race CMO Dr David Fuller said: *"The positive results from the first stage of this trial in such a heavily pre-treated relapsed or refractory Acute Myeloid Leukaemia population is encouraging, especially with three of the patients being subsequently bridged to transplant. We look forward to the next stage of this study which, together with data from the EMD AML Trial (RAC-006) which is soon to commence recruitment in Australia, is extending our understanding of Zantrene in a modern AML setting."*

Study Lead Prof Arnon Nagler said: *"The encouraging results of our Phase I study with* Zantrene *monotherapy and moreover the current Phase II study altogether with Zantrene in combination in extremely heavily treated advanced high risk AML patients are encouraging and may indicate a role for Zantrene in modern AML treatment paradigm to the benefit of our patients."*

Race Clinical Advisory Board Chair Prof Borje Andersson said: "*We are very excited about the positive data from the first stage of this trial in such a heavily pre-treated R/R AML population, and we now look forward to the next phase, where we expect to see more patients respond favourably and with a consistently tolerable side effect profile. It appears that bridging to transplantation with long-term disease control can be achieved with confidence, given we can since perceive that the side effects reverse within a few weeks of the course being completed.***"**

Relapsed or Refractory Acute Myeloid Leukemia

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

Up to 30% of adults with newly diagnosed AML fail to achieve CR after two courses of intensive chemotherapy.

Even when CR is achieved through intense chemotherapy, approximately half of the younger and 80% of the older patients, relapse. In both clinical situations, refractory and/or relapsed AML, active disease remains a major therapeutic challenge despite recent advances in the clinic.

Clinical Trial Design

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

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

A two-cohort dose escalation schema using a standard 3 + 3 design will be employed. Cohort 1 will enroll three patients to receive the FluCloZan regimen for four consecutive days. If no dose limiting toxicities (DLTs) have occurred in the first three patients by day 30 of their first cycle of treatment, then Cohort 2 will receive the treatment for five days (with the extra day representing dose escalation).

Phase 2, Expansion (Efficacy Stage)

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

Efficacy assessments will be based on bone marrow examination at a minimum of two time points on Day 21 and on Day 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 on peripheral blood hematology results during the treatment course and between Day 21 to 42.

Treatment will be 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 will be actively followed-up every three months for a further 12 months following completion treatment for disease free survival (DFS) and overall survival (OS).

Indicative Timelines

The Phase 2 stage of the trial is expected to take an additional 20 to 30 months to complete. Given the trial is open-label, Race expects data will be reported at interim points throughout the remainder of the trial.

Clinical Trial Summary

Study Title	An Open-label, Phase 1b/2, Two-stage, Study of Zantrene® (Bisantrene) in combination with Fludarabine and Clofarabine as Salvage Therapy for Adult Patients with Relapsed or Refractory Acute Myeloid Leukaemia (AML)
Registration	NCT04989335
Phase of Development	Phase 1b/2
Active Ingredient	Fludarabine, Clofarabine, Zantrene (bisantrene)(FluCloZan)
Study Description	Phase 1b/2 study of FluCloZan, IV, in cohorts of adult patients with R/R AML using a 2-stage design: a Phase 1b lead-in dose escalation stage to establish the MTD or RP2D of FluCloZan and a Phase 2 expansion stage to determine efficacy and confirm safety of the FluCloZan regimen at the RP2D.
Principal Investigator	Professor Arnon Nagler
Sponsor	Race Oncology
Indication/population	Adult men and women 18 to 65 years of age with relapsed and/ or refractory Acute Myeloid Leukemia (R/R AML) including those presenting with non-CNS extramedullary disease.
Number of Subjects	Phase 1b: up to 12 patients Phase 2: up to 17 patients in the expansion phase
Study Period	36 – 40 months
Study Design	A two-cohort dose escalation schema using a standard 3 + 3 design will be employed followed by an expansion phase at the RP2D. As the patient population is considered relapsed and/or refractory to existing treatments, a comparator arm will not be used.
Statistical methods	Simon 2 stage design
End Points	Primary: Phase 1b Dose Escalation: number of subjects experiencing a DLT in each cohort Phase 2 Expansion: Overall Response Rate (ORR) defined as the proportion of subjects with CR and Cri between Day 30 to Day 42 Secondary: Transplant/allo-HSCT rates (for transplant/allo-HSCT-eligible subjects); Combined CR and Cri and PR response rate; Morphologic leukemia-free state (MLFS); Partial remission (PR); Stable disease (SD); Progressive disease (PD); Relapse; Disease free survival (DFS); Overall survival (OS); Time to next treatment (for transplant/allo-HSCT-ineligible subjects)
Participating Centres	1 (Chaim Sheba Medical Center, Tel Hashomer, Israel)
Dates	First patient August 6, 2021; Last patient (anticipated): Q3 CY2023

Q&A

Is this a positive result?

Yes. While the data is limited due to the small number of patients treated to date, bridging half of these very heavily pre-treated patients to a stem cell transplant that offers them a chance of a cure is encouraging.

Why were such difficult to treat patients included in the trial?

Phase 1 oncology trials are difficult to recruit patients due to a lack of efficacy and safety data or knowledge of the optimal dosing. As a consequence, early-stage trials typically enrol patients with more advanced disease who have been exposed to greater numbers of prior treatments. Each cycle of treatment a cancer patient experiences and fails increases the risk of general resistance developing. For example, a treatment that may work in 70% of first line patients may only work in 5% of 6th line patients. As treatment rounds progress the patients become less and less likely to respond to any new treatment. They also at increased risk of serious side effects (such as infection) as they are weakened by the past treatments and the progression of the cancer.

How do the results compare to the earlier Phase 2 trial in Israel?

Patients in previous Phase 2 trial of Zantrene used as a single agent showed an overall clinical response rate of 40% (ASX Announcement: 16 June 2020). The patients in the early trial had a median of three prior lines of treatment. In the subgroup of patients from the current triple combination study who had received a similar number of prior treatment lines, the response rate appears higher (3 out of 4). It should be noted that due to the small number of patients treated to date, that this positive data should be seen as preliminary only.

References

1.Staber, P., Langner, S., Dornbusch, H. J. & Neumeister, P. Antifungal management in cancer patients. *Wien Med Wochenschr* **157**, 503–510 (2007).

2. Mellor, H. R. & Callaghan, R. Resistance to Chemotherapy in Cancer: A Complex and Integrated Cellular Response. *Pharmacology* **81**, 275–300 (2008).

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

About Professor Nagler

Professor Arnon Nagler MD MSc is Professor of Medicine at The Tel Aviv University, Director of the Division of Hematology at Sheba Medical Center, and Director of the Bone Marrow transplantation and Cord Blood Bank at Sheba Medical Center. He is the chair of the ALWP (Acute Leukemia Working Party) of the EBMT (European Bone Marrow Transplantation society), co-chair of the Scientific Council of the EBMT and serves on the Editorial Board of several Journals. He is one of the pioneers of the non-myeloablative and reduced intensity/toxicity allogeneic transplantations for malignant and non-malignant disorders. His interests include haematopoietic stem cell transplantation, haematological malignancies, cord blood biology and transplantation and immunotherapy. Prof. Nagler has written numerous original articles, reviews and chapters for peer-reviewed journals in the leukaemia field and is the principal investigator of multiple clinical studies including first in-human trials for novel agents, including pidilizumab and BL8040 (CXCR4 antagonist). He has received several awards and has made numerous presentations at all international transplantation and haematology meetings, including ASH, ASBMT/CIBMTR, EBMT and EHA.

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