RACE ONCOLOGY

ASX Announcement

Combining Bisantrene with Decitabine Significantly Enhances Killing of Multiple Cancer Cell Types

- **Bisantrene and decitabine used together offer significantly improved cancer cell-killing across a broad panel of 143 tumour cell lines than either drug used alone**
- **These results support the use of decitabine in combination with bisantrene as a potential treatment for many cancers, including solid tumours such as lung, prostate, pancreas, breast and head and neck cancer**
- **The Bisantrene/decitabine combination to be explored in a proposed Phase 1/2 investigator-initiated AML clinical trial.**

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14 May 2024 – Race Oncology Limited ("Race") is pleased to share the results from recent preclinical work performed under contract at Oncolines B.V. (Netherlands). In these studies, bisantrene was screened in combination with decitabine for enhanced anticancer activity across a broad panel of 143 cancer cell lines, representative of solid and blood cancers originating from more than 20 different human tissues.

Decitabine is a nucleoside analogue drug used in the treatment of some blood cancers, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), but it has not shown clinical efficacy in solid tumours[1]. In this study, decitabine was found to enhance the cell-killing activity of bisantrene across a comprehensive range of the most common human cancer types, including many solid tumours. Combining decitabine with bisantrene at clinically relevant concentrations significantly enhanced cancer cell-killing, with 92% (131 out of 143) of the cell lines showing improvement (p-value <0.0001). These results build on the impressive preclinical work Race completed in collaboration with the University of Newcastle, which found robust cancer killing synergy in cell and animal models of AML between bisantrene and decitabine (ASX Announcement: 06 March 2024). These new results suggest the clinical utility of decitabine could be expanded beyond blood cancers to solid tumours if used with bisantrene.

Race Chief Executive Officer, Dr Daniel Tillett comments: *"These results open exciting new treatment opportunities for both bisantrene and decitabine. While decitabine has proven its effectiveness in haematological cancers, it has not demonstrated clinical utility in solid tumours, like lung or breast cancer. This new body of work is highly supportive of the results from the University of Newcastle in preclinical AML models using a combination of bisantrene and decitabine. Thanks to the continued support of our shareholders, we are looking forward to announcing a clinical trial of this promising anticancer drug combination in the near future."*

Study Highlights

Background

Race has previously reported that when tested against a panel of 143 cancer cell lines representing more than 20 human tumour types, bisantrene was able to kill over 79% of the cells at clinically achievable drug concentrations (ASX Announcement: 21 September 2023). Further, when the cancer cells were treated with mixtures containing bisantrene and the widely used, standard-of-care chemotherapy drug doxorubicin, greater cell-killing was seen in 86% of tumour cells relative to doxorubicin alone. In the current study, bisantrene was tested in the same 143 cancer cell panel in combination with the DNA hypomethylating agent, decitabine.

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Combining decitabine with bisantrene increases killing of diverse human solid and blood cancer cells.

Decitabine (5-aza-2′-deoxycytidine) is an anticancer drug that functions as a DNA methyltransferase inhibitor, leading to DNA hypomethylation, reactivation of epigenetically silenced tumour suppressor genes, and other anticancer effects[2]. Decitabine has been approved for the treatment of the haematological (blood) cancers myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Therapies using decitabine in combination with other chemotherapy drugs, immunotherapies and targeted treatments in blood cancers continues to be an area of active clinical study. The successful use of decitabine for treating blood cancers has spurred interest in extending its use into solid tumours. However, despite several decades of preclinical and clinical research, confirmation of efficacy using decitabine combinations in solid tumour therapy remains elusive[1].

When tested in combination with bisantrene against 143 different cancer cells, decitabine was found to improve cell-killing.

Figure 1 shows that on its own, decitabine treatment (blue curve) had limited effects on the viability of eight representative solid tumour cell lines. As has been described previously, bisantrene was found to be an effective agent in these eight cell lines with IC_{50} values ranging from 73-926 nM (red curves). Importantly, when decitabine was added to bisantrene the cell-killing activity of the combination was significantly enhanced.

Similar effects were seen across the whole panel of cancer cell types, with 56% of the cell lines showing >2-fold increases in activity for the combination, relative to bisantrene alone, and 36% showing up to 2-fold improvements (Figure 2). Only 8% of the cell lines showed no improvement in cell-killing activity for the combination. Interestingly, the enhanced cell-killing effects appeared to be stronger in solid tumour cell lines compared to blood cancer cell lines (myeloid and lymphoid lines) where decitabine shows clinical efficacy.

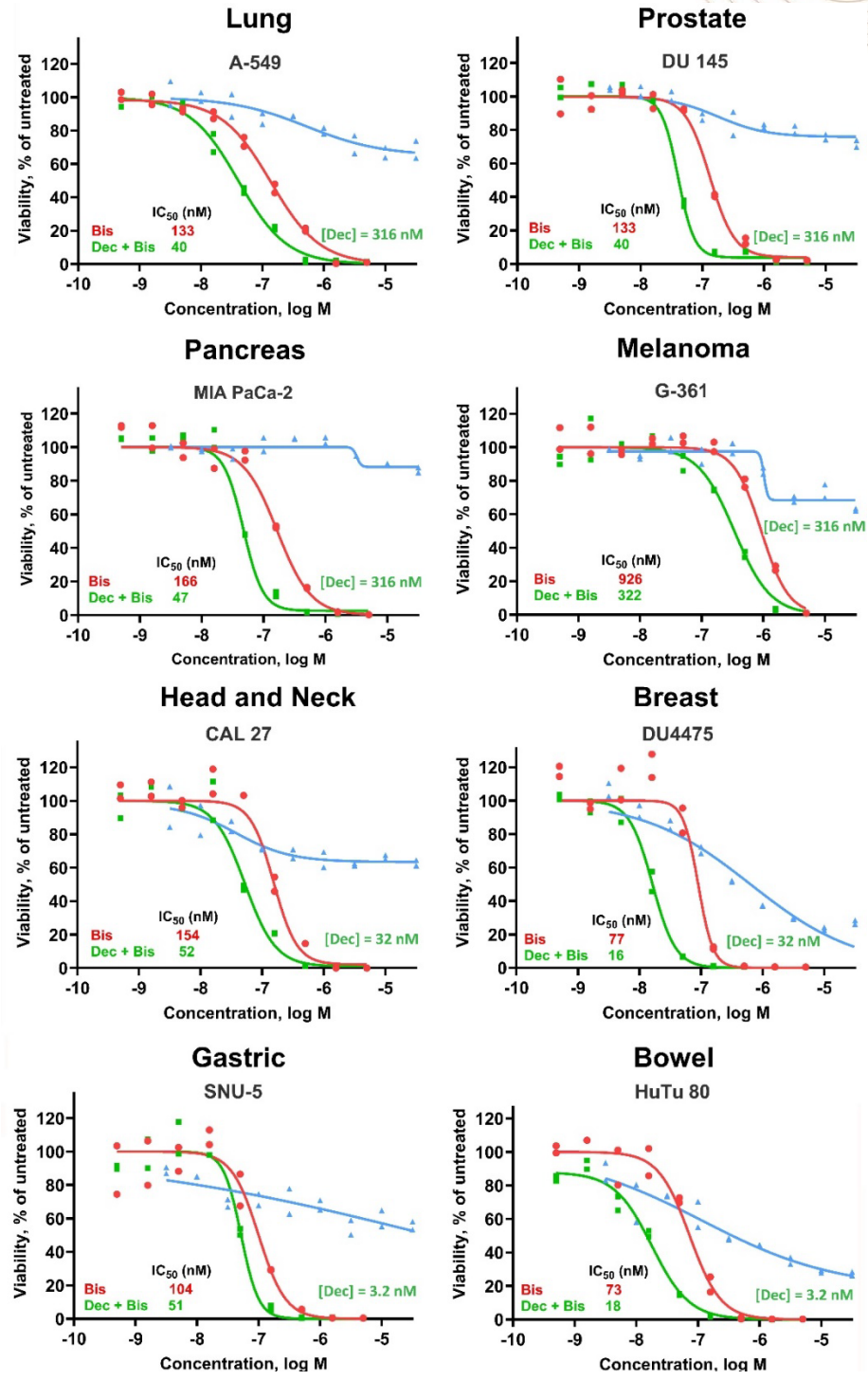

Figure 1. Viability of human cancer cells representing eight different solid organ tumour types following treatment with decitabine (Dec, blue), bisantrene (Bis, red) or the combination of decitabine + bisantrene (Dec + Bis, green). The concentration of decitabine [Dec] used in the combination experiment was approximately equal to the IC_{20} of decitabine when used alone against each cell line (blue curve).

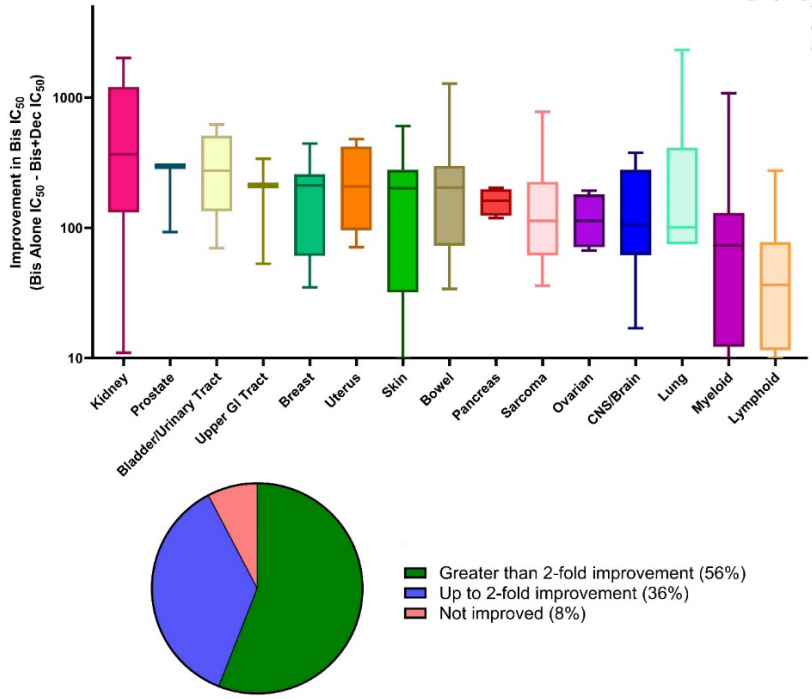

Figure 2. Combining decitabine with bisantrene improves cell-killing activity across diverse tumour types. *Top:* The half-maximal inhibitory concentration (IC_{50}) was determined for bisantrene (Bis) alone and the bisantrene/decitabine (Bis+Dec) combination against 143 cancer cell lines derived from diverse solid and haematological human tumours. The difference between the IC_{50} values for bisantrene and the combination (Bis alone IC_{50} – Bis + Dec IC_{50}) was plotted for each tumour type. Numbers > 0 indicate improved cell-killing for the combination versus bisantrene alone. Boxes show the 25-75% range, with the line within each box representing the median change in IC_{50} value. The upper and lower edges of the boxes represent the 75th and 25th percentiles, respectively. Whiskers show the minimum and maximum change in IC_{50} values observed for each cancer cell type. ***Bottom:*** The proportion of cell lines showing improved (i.e. lower) IC_{50} values when comparing bisantrene/decitabine combination treatments to bisantrene alone. A significant reduction (improvement) was observed in the IC_{50} of cells treated with decitabine + bisantrene compared to bisantrene alone, $p<0.0001$. A 2-fold improvement represents a 50% reduction in IC_{50}. Statistical analysis was performed using a non-parametric Wilcoxon matched-pairs signed rank test.

Next Steps

- Optimisation of the combination dosing through *in vivo* preclinical studies and identification of the best clinical treatment opportunities.
- Further preclinical studies to determine the cellular mechanism(s) responsible for the enhanced cancer cell killing observed with the bisantrene and decitabine combination.
- Publication of the completed data package in a high-quality, international, peer-reviewed journal.
- Announcement of Race supporting clinical studies utilising bisantrene in combination with decitabine to improve outcomes for cancer patients (subject to shareholder support).

Q&A

What does this result mean for future clinical trials of bisantrene?

The results of this study suggest that the combination of bisantrene and decitabine may have broad clinical utility across the solid tumour landscape. Race will continue to critically evaluate all opportunities in this space from both a commercial and scientific perspective.

What is the commercial significance of this discovery?

This discovery expands the potential clinical use of decitabine beyond haematological (blood) cancers into solid tumour therapy by combination with bisantrene. The combination may be of interest to the owners of marketed formulations of decitabine, including oral decitabine.

How soon can this combination of bisantrene and decitabine be tested in patients?

Race has received strong interest from a leading Australian haematologist to undertake an investigator-initiated Phase 1/2 AML clinical trial utilising RC220 bisantrene in combination with an oral decitabine in up to 60 AML patients who are unable or unwilling to undertake high intensity chemotherapy. Funding support for this trial is contingent upon Race shareholder support via the bonus option issue (ASX Release 22 November 2023). Race will update investors shortly on support for this trial.

References

1. Chenlin Ye, Nan Jiang, Jing Zheng, Shumeng Zhang, Jingchen Zhang, Jianya Zhou. Epigenetic therapy: Research progress of decitabine in the treatment of solid tumors. *BBA - Reviews on Cancer.* **2024**, 1879, 189066.

2. Nicholas J. Short, Hagop Kantarjian. Hypomethylating agents for the treatment of myelodysplastic syndromes and acute myeloid leukemia: Past discoveries and future directions. *Am. J. Hematol.* **2022**, 1-11.

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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, bisantrene, is a small molecule chemotherapeutic. Bisantrene has a rich and unique clinical history with demonstrated therapeutic benefits in both adult and paediatric patients, a well-characterised safety profile, and compelling clinical data demonstrating an anticancer effect and less cardiotoxicity over certain anthracyclines, such as doxorubicin.

Race is advancing a reformulated bisantrene (RC220) to address the high unmet needs of patients across multiple oncology indications, with a clinical focus on anthracycline combinations, where we hope to deliver cardioprotection and enhanced anti-cancer activity in solid tumours. Race is also exploring RC220 as a low-intensity treatment for acute myeloid leukaemia.

Race is investigating the effect of bisantrene on the m^6A RNA pathway, following independent research published 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 as a driver of a diverse range of cancers.

Race Oncology has collaborated with Astex, City of Hope, 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 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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