20 May 2026 Sydney, Australia

Xolatryp® Enhances Anthracycline Anti-Tumour Efficacy

Highlights:

- Nyrada's lead drug candidate Xolatryp® demonstrates clear anti-tumour activity in a preclinical model of liver cancer, both as a monotherapy and in combination with doxorubicin.
- The combination with doxorubicin exhibited the greatest reduction in tumour volume and was well tolerated.
- A provisional patent application for Xolatryp as an anti-cancer agent has been lodged, complementary to Nyrada's earlier allowed composition of matter patent application.

Nyrada Inc (ASX:NYR), a clinical-stage biotechnology company focused on developing Transient Receptor Potential Canonical (TRPC) ion channel inhibitors to treat a range of medical conditions, today provides results of a preclinical oncology study.

The Model

Published literature is increasingly highlighting the role that TRPC channels play in the regulation of cancer progression[i]. TRPC6-mediated calcium signalling has also been implicated in multidrug resistance in hepatocellular carcinoma cells[ii] (liver cancer), supporting a role in chemotherapy response.

Xolatryp, a potent inhibitor of TRPC3/6/7 ion channels, was evaluated in a Huh7 cell-line derived rodent xenograft model of liver cancer, a standard preclinical model to assess tumour growth inhibition.

Huh7 cells were implanted subcutaneously, and treatment was initiated once the tumours reached 50 - 75 mm^3 (marked Day 0). Animals received either:

- vehicle control,
- doxorubicin, a clinically approved first-line chemotherapy drug, administered twice weekly,
- Xolatryp, administered intratumorally once daily, or
- a combination of doxorubicin with Xolatryp.

Tumour volumes were measured every other day for two weeks post-treatment initiation. Body weight and general animal health assessments were undertaken daily. Plasma cardiac troponin I levels were measured to assess heart health, which is often worsened in cancer patients receiving doxorubicin treatment[iii,iv].

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Doxorubicin

Doxorubicin is a potent anthracycline chemotherapy drug, widely used as a first-line treatment for both solid and metastatic tumours. It is often used in combination with other agents and forms part of the standard regimen in treating liver cancer, breast cancer, leukemias, lymphomas (Hodgkin's and non-Hodgkin's), sarcomas (bone and soft tissue), and bladder, lung, and ovarian cancers, among others. In use since the 1970s, doxorubicin is considered a "backbone drug" in oncology.

Study Results

The combination of Xolatryp with doxorubicin produced the greatest anti-tumour effect in this model, showing a 57 per cent reduction in tumour volume compared with vehicle control at Day 14. This compares with a 41 per cent reduction observed with doxorubicin monotherapy. This result, with combination treatment, represents an approximately 39 per cent improvement in anti-tumour activity relative to doxorubicin alone, consistent with an additive effect.

Xolatryp also demonstrated activity as a monotherapy, with a 32 per cent reduction in tumour volume relative to vehicle control. This effect is consistent with the modulation of calcium-dependent survival pathways associated with TRPC channel activity in cancer cells[v,vi].

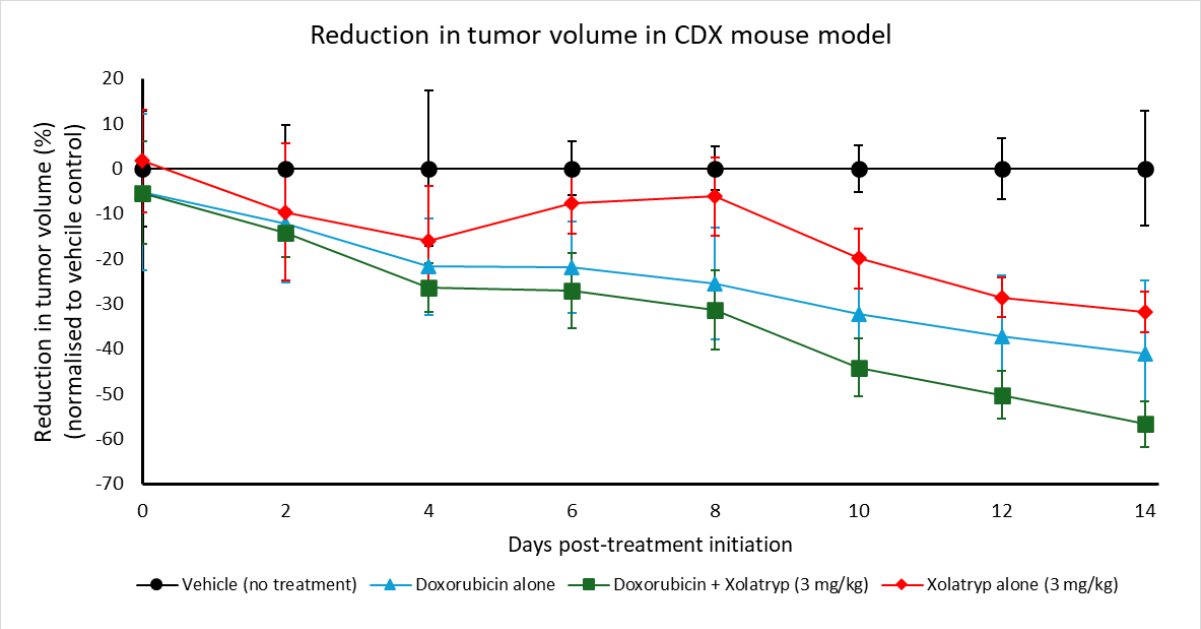

Figure 1. Per cent reduction in mean tumour volume (± standard deviation; n = 6 animals per group per timepoint, except n = 4 doxorubicin + Xolatryp at Day 14).

Figure 2 shows the mean tumour volumes over the two-week treatment period. Significant tumour growth reduction was observed as early as Day 4 in the combination group (p = 0.015)[1] and this statistically significant reduction was maintained through the study endpoint.

Doxorubicin monotherapy demonstrated significant tumour reduction from Day 6 onwards (p = 0.0006)[1], while Xolatryp monotherapy demonstrated significant reductions from Day 10 (p = 0.003)[1].

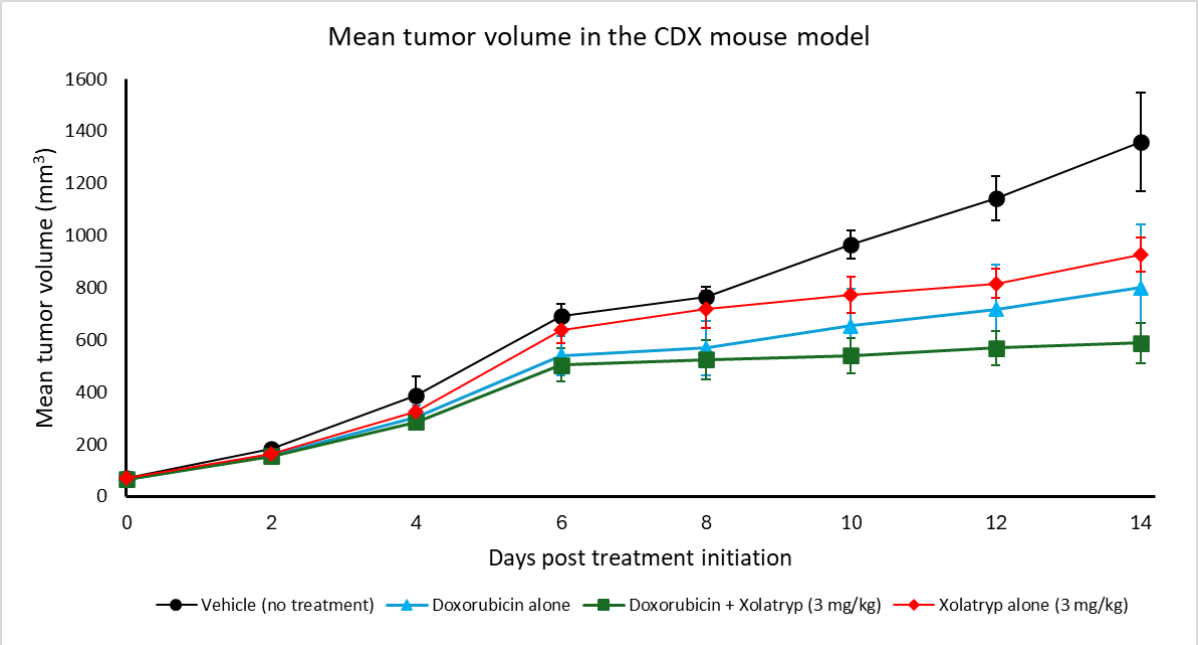

Figure 2. Mean tumour volumes (± standard deviation; n = 6 animals per group per timepoint, except n = 4 doxorubicin + Xolatryp at Day 14).

Safety Observations

Overall animal health, based on body weight, was broadly consistent with expectations for this model (Figure 3). Two animals in the Xolatryp plus doxorubicin group died prematurely, consistent with tumour lysis syndrome (TLS), a recognised clinical effect in which rapid tumour cell death causes metabolic disturbances. TLS is associated with highly active anti-cancer therapies and can be managed in the clinic.

[1] p-value calculated at individual timepoints using one-way ANOVA with Holm-Sidak post-hoc multiple comparisons versus vehicle control; n = 6 per group.

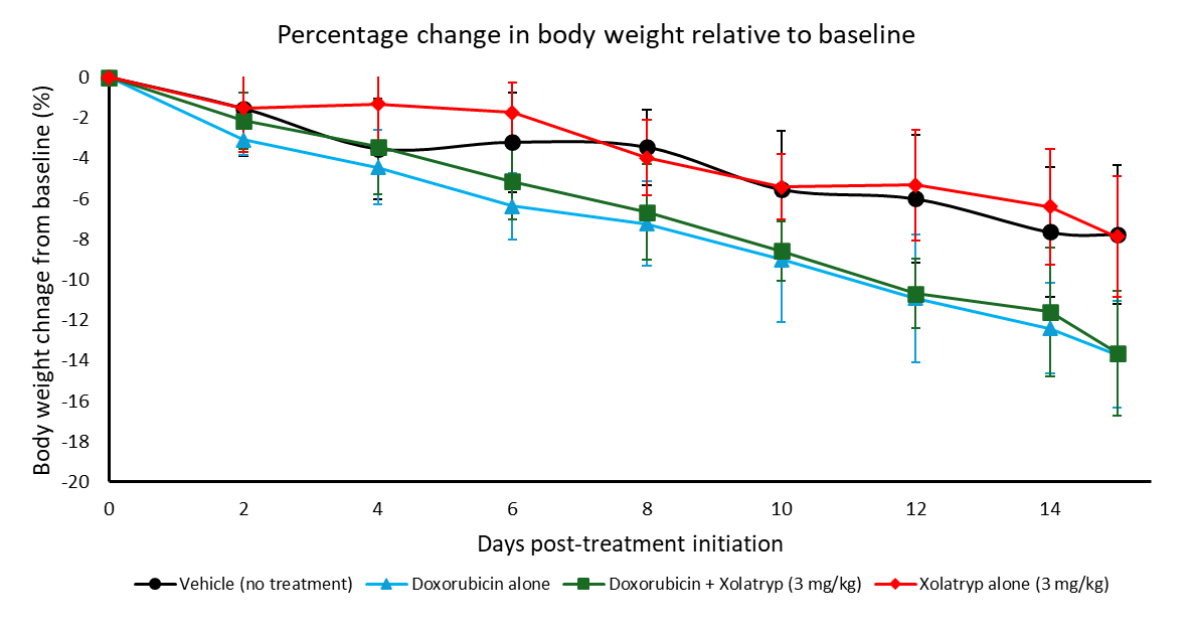

Figure 3: Mean body weight change from baseline (± standard deviation; n = 6 animals per group per timepoint, except n = 4 doxorubicin + Xolatryp at Day 14).

In addition, animals receiving Xolatryp, both as a monotherapy and in combination with doxorubicin, demonstrated a favourable trend in cardiac troponin I levels relative to doxorubicin alone.

Conclusion and Next Steps

Taken together, these findings demonstrate that Xolatryp exhibits anti-tumour activity both as a monotherapy and in combination with doxorubicin, with the combination treatment showing earlier onset and greater magnitude of tumour growth inhibition in the Huh7 CDX model. The data support further preclinical evaluation of Xolatryp across additional tumour types where anthracyclines remain standard-of-care therapy, as well as assessment in combination with other clinically relevant anti-cancer agents. Future studies will also focus on clinically translatable systemic dosing strategies to optimise anti-tumour efficacy while maintaining tolerability.

An additional preclinical cardiomyopathy study is being undertaken to further assess the potential of Xolatryp to mitigate doxorubicin-associated cardiac injury and support the development of Xolatryp as a differentiated adjunct therapy for use alongside anthracycline based chemotherapy.

A patent application covering the use of Xolatryp as an anti-cancer agent has been lodged, complementary to Nyrada's earlier allowed composition of matter patent application.

Nyrada Managing Director and CEO James Bonnar commented: "This study demonstrates highly encouraging proof-of-concept of a clear additive benefit over a standard-of-care treatment, consistent with enhanced anti-tumour activity of doxorubicin when combined with Xolatryp.

"The results support the potential of Xolatryp to improve therapeutic outcomes in cancer patients treated with anthracycline drugs."

About Xolatryp

Xolatryp is a small-molecule inhibitor of TRPC3/6/7 channels designed to limit excessive Ca^{2+} entry related to multiple disease pathologies.

A Phase I clinical trial to assess the safety, tolerability, and pharmacokinetics has been successfully completed and a Phase IIa clinical trial has commenced to assess the safety and preliminary efficacy of Xolatryp in reducing myocardial ischemia reperfusion injury in patients with ST-Elevation Myocardial Infarction (STEMI) undergoing PCI.

– ENDs –

References:

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About Nyrada Inc.

Nyrada Inc. is a clinical-stage biotechnology company focused on the discovery and development of innovative small-molecule therapies, specifically targeting Transient Receptor Potential Canonical (TRPC) ion channels. The company's lead candidate, Xolatryp®, has shown efficacy in preclinical cardioprotection and neuroprotection models and has completed a first-in-human Phase I clinical trial. A Phase IIa clinical trial has commenced to assess the safety and preliminary efficacy of Xolatryp in reducing myocardial ischemia reperfusion injury in patients with ST-Elevation Myocardial Infarction (STEMI) undergoing PCI. Nyrada Inc. (ARBN 625 401 818) is incorporated in Delaware, US, with limited liability for its stockholders.

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