Diffuse large B cell lymphoma (DLBCL) is the most common subtype of aggressive lymphoma, for which the standard-of-care treatment is rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Although the majority of patients respond to R-CHOP around 40% relapse after first line treatment. Inability to tolerate or maintain dose-intensity of the anthracycline doxorubicin increases relapse risk after R-CHOP treatment. A key side effect of doxorubicin that contributes to its poor tolerance especially in the elderly is its cardiotoxicity. Thus, the development of anthracycline derivatives which retain anti-cancer properties but show reduced cardiotoxicity could have an impact in the treatment of DLBCL. Camsirubicin (MNPR-202, GX-150), a monoparacic 13-deoxysacorubicin analog which retains the non-cardiotoxic backbone but is modified at other sites, which may enable it to evade doxorubicin drug resistance mechanisms.

We performed a comparative in vitro study between doxorubicin and MNPR-202 to evaluate the feasibility of substituting doxorubicin with this novel compound. By treating 8 DLBCL cell lines (1C, SU-DHL-2, SU-DHL-4, SU-DHL-6, OCI-Ly3, OCI-Ly8, HT, and DGHM2) with either doxorubicin or MNPR-202, we compared broad phenotypes such as cell proliferation, extent of apoptosis, and DNA damage. We determined through Cell Titer Blue assays that doxorubicin and MNPR-202 had similar effects on cell proliferation and comparable IC50s. Interestingly, with 24-48 hours of drug exposure, MNPR-202 appeared to be more potent in inducing apoptosis as indicated by Annexin-PI staining. Western blot analysis for γ-H2AX, a marker of DNA damage, also demonstrated increased DNA damage after MNPR-202 treatment relative to doxorubicin.

Next, we compared activation of immunomodulatory innate immune response genes of the cGAS/STING and RIG-I pathways by doxorubicin and MNPR-202, using qPCR of interferon stimulated genes after drug treatment in lymphoma cells. In contrast to doxorubicin and MNPR-202, using qPCR of interferon stimulated genes after drug treatment in lymphoma cells. In contrast, MNPR-202 did not.

Finally, in an effort to determine potential synergistic compounds MNPR-202 could be combined with to enhance efficacy, we performed a drug screen with a library of approximately 200 compounds. This screen revealed distinct differences in the synergy profile between doxorubicin and MNPR-202. For example, a clear antagonistic effect on cell killing was seen between PLK1 inhibitor, volasertib, and doxorubicin, but not volasertib and MNPR-202, this antagonism was seen to a significantly lesser extent.

Taken together, these findings indicate that doxorubicin and MNPR-202 overall have a similar cytotoxic potency, but likely work through distinct cellular pathways. MNPR-202 appears to induce more DNA damage and less ancillary innate immune activation. These intracellular differences also influence drug synergies observed with the two chemotherapeutics, implying that in the context of certain combinatorial regimens, MNPR-202 may be superior to doxorubicin. Overall these findings suggest promise for further in vivo and clinical evaluation of MNPR-202 as a potentially effective yet non-cardiotoxic anthracycline derivative in lymphoma.