Background Plinabulin is a selective immunomodulating microtubule-binding agent that exerts direct anti-cancer activity as a single agent, as well as enhancing the immune response, primarily by inducing dendritic cell (DC) maturation and T-cell activation (Kashyap 2019; Natoli 2021). Radiation can liberate local antigen release, and when coupled to DC maturation, can potentiate systemic immunity with immune checkpoint inhibitors (ICI), even in ICI-refractory settings. Here we test this hypothesis preclinically and clinically in a phase I basket study.

Methods In vitro assays involved combining plinabulin with radiation in different timings before and after radiation. DC activation was assessed with flow cytometry evaluating CD80/CD86/MHC-II expression. Using syngeneic TSA breast cancer model, we irradiated tumors with 8Gy x 3, and treated them with or without plinabulin and/or αPD1. We initiated an open-label, single-center, phase I study to evaluate the safety of plinabulin in combination with radiation and immunotherapy in patients with select advanced malignancies and a majority had progressed on PD-1, PD-L1 and/or CTLA-4 targeted antibodies (NCT04902040).

Results In SP37A3 and XS106 DC lines, we found that DC maturation was enhanced by combining radiation with plinabulin, particularly when radiation was added 3–6 hours prior to plinabulin, but not when plinabulin was added first before radiation. In the TSA model, there were minimal anti-tumoral effects with αPD1 alone, plinabulin alone, and αPD1+plinabulin. However, triple therapy triggered a stronger abscopal effect than irradiation plus αPD1. The percentage of CD8+ T cells and CD86+ DCs in the tumor were significantly increased in the triple combination group that were not seen for the monotherapy or bimodal therapy groups (p<0.05, Dunnett’s test). We initiated a phase I trial testing the triple combination approach and have enrolled six tumor types with ten ICI-refractory patients (PD-1/PD-L1, CTLA-4). Eight patients received at least 3 cycles with no dose-limiting toxicities. Per RECIST criteria, there were 8 responders and 2 non-responders. In responders, whole blood analyses indicate positive trends towards increased mDC numbers and maturation markers (CD40/CD80/CD83/CD86), increased CCR7 expression on pDC, and monocyte shift from classical to inflammatory phenotype. Single-cell RNAseq analysis of tumor biopsies at pre/post treatment indicates activation of a GEF-H1-dependent immune signature in subtypes of DCs and monocyte-derived macrophages in responder patients.

Conclusions Plinabulin in combination with radiation and ICI was able to induce systemic immune response in immunotherapy-refractory tumors, possibly by enhancing the coactivation of DCs to generate a systemic immune response.