TRIPLE-DRUG ORAL IMMUNOTHERAPY TARGETING MYELOID CELLS FOR TREATMENT OF METASTATIC OSTEOSARCOMA EVALUATED IN SPONTANEOUS CANINE MODEL

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Background We reported recently in a spontaneous canine model of metastatic osteosarcoma (OS) that oral treatment with two repurposed agents targeting monocyte migration (losartan) and MDSC and Tregs (toceranib) induced partial responses in 4/16 dogs (25%) with another 4 dogs experiencing durable stable disease (SD), for a clinical benefit rate of 50%. In the current study, we evaluated the utility of incorporating ladarixin (an orally bioavailable allosteric CXCR1/2 antagonist) into the losartan/toceranib regimen in 15 dogs with OS metastatic to the lungs.

Methods The effects of treatment on lung metastases, circulating cytokine concentrations, and gene expression profiles in PBMC were assessed in this new study. Studies are also ongoing to determine whether this same approach has activity in the adjuvant setting in dogs with appendicular OS treated prior to and continuously following amputation, in lieu of standard cytotoxic adjuvant chemotherapy. To date, 18 animals have been enrolled in the adjuvant trial, and analysis of the impact on MFI and OST are ongoing as data matures.

Results Of enrolled dogs with greater than 60 days of follow up, 1 dog underwent a complete response (400+ days) and another 4 dogs experienced PR, for an objective response rate of 36%; another 5 dogs exhibited durable SD, for an overall clinical benefit rate of 71%. The 3-drug protocol was generally well-tolerated, with no adverse events other than those associated with toceranib alone (gastrointestinal signs). Transcriptomic analysis of PBMCs from 8 dogs on days 0 and 14 using Nanostring revealed significant downregulation of 30 immune genes, including IRF2, IRF8, CTLA4, NFKB, and CCR2, and upregulation of 176 genes, including IL21, CCL19, B7-H3, IL17A/B. Pathway analysis demonstrated significant downregulation of IFN-γ and IFN-α response pathways, and upregulation of β-catenin signaling pathways.

Conclusions In summary, these findings in a canine spontaneous osteosarcoma model indicate that the combined losartan/ладарixin/toceranib immunotherapy protocol is biologically active and can effectively modify the immune suppressive tumor microenvironment to generate spontaneous antitumor activity in dogs with advanced OS-lung metastases.