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Abstract 3251: **The immunostimulatory effect of 9-ING-41, a small molecule GSK-3 inhibitor, in sarcomas**

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Abstract

Due to the rarity and genomic disparity of soft tissue and bone sarcomas, actionable therapeutic targets have been elusive. However, inhibition of GSK-3β has emerged as a potentially promising therapy that could be of great benefit to pediatric and adult sarcoma patients. Saos-2 osteosarcoma and 93T449 liposarcoma cell lines were pretreated at $IC50_{72}$ with small molecule GSK- 3β inhibitor 9-ING-41 (elraglusib). The cells were harvested for western blot analysis after 48 hours of treatment. Additionally, both cancer cell lines as well as TALL-104 T-cells and NK-92 NK cells were treated with 0.5 μM 9-ING-41 for 24 hours and harvested for Luminex cytokine profiling. The western blots demonstrated an increase in cPARP, an apoptotic marker, in both cancer cell lines after 9-ING-41 treatment. Additionally, an increase in PD-L1 expression was observed. The cytokine analysis revealed stimulation of immune cell activity in response to 9-ING-41. Treated T-cells had an increase in CXCL11, which is associated with T-cell recruitment, as well as an increased level of IL-18, which is shown to induce increased IFN-γ in Th1 cells. Additionally, NK-92 cells demonstrated an increase in IL- 8 chemokine and an increase in soluble TRAIL (TRAIL/TNFSF10). The cancer cell lines showed a homogenous increase in growth factor TGF-α, however, only the Saos-2 osteosarcoma cell line demonstrated an increase of IL-6. We are further validating the data with follow-up cytokine profiling. The increase in immunostimulatory cytokines as well as the increased expression of PD-L1 suggest a rationale for combining 9-ING-41 with immune checkpoint blockade therapy. The potential synergistic effect of these two therapies is currently under investigation with co-culture experiments of sarcoma and immune cells. The treatment cohorts for these experiments include 9-ING-41 combined with either anti-PD-L1, anti-PD-1, or anti-CTLA-4 immune checkpoint inhibitors. Our results suggest a promising combination therapeutic strategy for patients with soft tissue and bone sarcomas and future work will strive to better elucidate the mechanisms of efficacy.