1442 EXPLORING NOVEL FERROPTOSIS INDUCER AS A PROMISING STRATEGY FOR SARCOMA TREATMENT

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Background Sarcomas constitute a diverse group of tumors with mesenchymal origin. Mesenchymal phenotype was previously published to render cancer cells vulnerable to ferroptosis, a form of cell death that is characterized by excessive lipid peroxidation. This is presumably due to higher levels of polyunsaturated fatty acid in cellular membranes compared with epithelial tissues. Analysis of public database has further revealed the dependency of various sarcoma subtypes on GPX4, an enzyme that converts lipid peroxides into innocuous lipid alcohols. These findings prompted us to investigate the possibility of targeting sarcomas with our novel proprietary inducer of ferroptosis.

Methods We initially identified compound 101 based on its target specificity, cellular potency, mouse blood stability and plasma pharmacokinetic properties. Viability, cell death and lipid peroxidation were evaluated upon treatment with compound 101 in two human sarcoma cell lines, HT1080 (fibrosarcoma) and SJCRH30 (rhabdomyosarcoma). Release of DAMPs HMGB1 and extracellular ATP (eATP) was assessed in human and murine cell lines treated with compound 101. Plasma levels and antitumor efficacy were evaluated in HT1080 and SJCRH30 CDX models in immunodeficient mice following repeated dosing with compound 101.

Results The compound 101 potently reduced viability, induced cell death and lipid peroxidation in both cell lines. Cell death due to ferroptosis was ascertained by co-treatment with ferroptosis inhibitor, ferrostatin-1 (Fer-1), which blocked compound-induced effects in all assays. Dosing with compound 101 resulted in significant target exposure and tumor growth inhibition in both CDX models. We benchmarked the efficacy against pazopanib, an approved agent in soft tissue sarcomas, which elicits anti-tumor effect by direct cytostatic and anti-angiogenic mechanisms. We found that our compound has an improved efficacy compared with pazopanib. Whether ferroptosis inducers are immunogenic is an open area of investigation. We found that cell lines release both DAMPs upon treatment with compound 101, suggesting that it causes immunogenic cell death. To address whether the *in vivo* efficacy with our compound could be further improved by administering it in mice with intact immune system, we are currently investigating it in syngeneic mouse models.

Conclusions In summary, our novel ferroptosis inducer shows sustained plasma levels and leads to significant tumor growth inhibition in fibrosarcoma and rharbomyosarcoma CDX models. Our findings highlight the potential of inducing ferroptosis as a promising strategy in sarcomas. Further investigations are warranted to validate our ferroptosis inducers as a therapeutic approach in sarcoma patients.

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