Increasing evidence highlights the diverse functions of extracellular vesicles (EVs) as intercellular messengers in all facets of cancer progression, pointing towards a potential new avenue in cancer treatment. Limited understanding of tumor-specific deregulations and lack of suitable drug compounds have hampered clinical translation of targeted interference with EV signaling. The most aggressive types of intracranial ependymoma (EPN) in children and adults are resistant to chemotherapy. Despite enormous diagnostic advancements in classification and stratification, EPN lacks recurrent effective molecular targets precluding access of affected patients to precision-based oncology therapeutics. Here, we characterized the proteome and transcriptome of EPN upon reduction of EV release. This study showcases the inhibition of EV signaling as a promising therapeutic strategy against mesenchymal tumor persisters, which are the suspected origins of repeated EPN relapses. Our study provides a framework to leverage cell state-specific vulnerabilities and drug repurposing to attack the most aggressive cell populations in cancers with unfavorable prognosis.