Abstract

Synovial sarcomas express the SSX-SS18 fusion oncoprotein, which drives tumorigenesis by compromising the function of the BAF (BRG1/BRM-associated factors) chromatin remodeling complex. Cells with this form of BAF perturbation are heavily dependent on the non-canonical BAF (ncBAF) subunit BRD9 (Bromodomain-containing protein 9) for survival. However, the mechanism by which BRD9 promotes tumor growth is not well understood. FHD-609 is a heterobifunctional degrader of BRD9 that is currently in clinical development for the treatment of advanced synovial sarcoma. Assays to measure the abundance of BRD9 protein in patient tumors will be important for demonstrating target engagement with FHD-609. Additionally, because tumor biopsies occur infrequently, assays to monitor BRD9 levels in peripheral tissues may permit longitudinal analysis of BRD9 degradation in patients treated with FHD-609. The objectives of the present study were to develop clinically relevant assays to quantify BRD9 protein levels in tumor and peripheral blood mononuclear cells (PBMCs), profile the pharmacodynamics (PD) of FHD-609 in these tissues, and to explore the downstream impacts of BRD9 degradation in synovial sarcoma.

Methods

Female nude mice bearing SYO-1 xenografts were treated with vehicle or FHD-609 at the indicated doses and schedules shown in Figure 2. Serum was collected at indicated timepoints post last dose. Complete degradation between doses is required for maximal antitumor efficacy.

Conclusions

• Newly validated IHC and flow cytometry assays demonstrate excellent sensitivity and specificity for BRD9 in tumor tissue and PBMCs, respectively.
• Target degradation in tumors is rapid and robust, but complete degradation is required between doses for maximal efficacy.
• PBMCs are an effective surrogate for target engagement in tumors.
• FHD-609 treatment decreases Myc expression and related gene sets, and decreases markers of proliferation in tumors in vivo.

References and Acknowledgements


We wish to thank the patients, clinicians and investigators for their participation in the Phase 1 clinical trial of FHD-609.