INTRODUCTION

- Bromodomain containing protein 9 (BRD9) is a unique subunit of the non-canonical Brahma-associated factor (ncBAF) chromatin remodeling complex.
- FHD-609 is a potent, selective, heterobifunctional degrader of BRD9 investigated in BRD9-dependent cancers, including synovial sarcoma and SMARCB1-loss tumors.
- BRD9 and associated biomarkers were evaluated in paired screening and on-treatment tumor biopsies. Tumors were also evaluated for cellular and tissue morphology changes.
- Kinetics of BRD9 degradation were assessed in peripheral blood mononuclear cells (PBMCs).
- RNA-sequencing was performed on patient tumor tissue to explore mechanistic impacts of prolonged BRD9 degradation.

RESULTS

Target engagement in patient tumor tissue assessed with BRD9 and associated biomarkers

BRD9

K67

c-Myc

SS18-SSX

Figure 1. Screening and on-treatment tumor biopsies were analyzed by immunohistochemistry (IHC). Shown are representative images from a subject in the 80 mg BIW dose cohort. Scale bar = 100 μm.

Figure 2. Tumor biopsies were collected at screening and on-treatment. BRD9 protein levels were scored by a pathologist (H-score). Each bar represents the change in BRD9 H-score relative to screening for an individual patient biopsy.

Complete BRD9 degradation observed at ≥ 40 mg BIW

Figure 3. A) BRD9 was analyzed in patient PBMCs by flow cytometry. Shown are plots of the T-cell (CD3+) population, which was found in preclinical studies to be the best tumor surrogate (Ref. 2). Values are mean fluorescence intensity (MFI) relative to each individual patient’s C1D1 pretreatment baseline. Data points represent dose group averages. B) BRD9 tumor H-scores for all screening and on-treatment biopsies. Days post-dose represent the total days since the most recent dose before biopsy collection.

Histology changes observed in some cases

Figure 5. Hematoxylin and eosin stained paired tumor biopsies. Top row: On-treatment biopsy shows fenestrated architecture. Bottom row: On-treatment biopsy shows cell dropout and increased collagenous stroma, suggesting decreased tumor density. Note: cells with altered morphology retained SS18-SSX positivity, indicating they are SS tumor cells (not shown). Scale bar = 100 μm.

CONCLUSIONS

- FHD-609 treatment led to dose-dependent BRD9 degradation in tumor tissue.
- Complete degradation observed beginning at BIW doses of 40 mg and above.
- Degradation maintained between doses, as assessed in peripheral blood and tumors collected several days post-dose.
- Reduced markers of proliferation and histological changes observed, including decreased cellularity in some cases, suggestive of reduced tumor density.
- Downregulation of gene sets associated with oncogenic growth and proliferation.

References and acknowledgements

3. Livingston, J. A. et al. CTOS Annual Meeting (2023)

We would like to formally thank the patients, families, co-investigators, and all study personnel for their contributions and participation in the trial.