PHARMACODYNAMICS AND MECHANISTIC IMPACTS OF FHD-609, A BRD9 DEGRADER, IN A PHASE 1 STUDY IN PATIENTS WITH ADVANCED SYNOVIAL SARCOMA OR SMARCB1-LOSS TUMORS

Mike Collins[1], Ariel Lefkovith[1], Jessica Wan[1], Kim Horrigan[1], Salih Topal[1], David L. Lahr[1], Alex Ballesteros-Perez[2], Alexander J. Lazar[3], Kathleen Healy[1], Sarah Reilly[1], Samuel V. Agresta[1], Scott Innis[1], Jessica Piel[1]

[1]Foghorn Therapeutics Inc, Cambridge, MA; [2]Certara Integrated Drug Development, Princeton, NJ; [3]The University of Texas MD Anderson Cancer Center, Houston, TX

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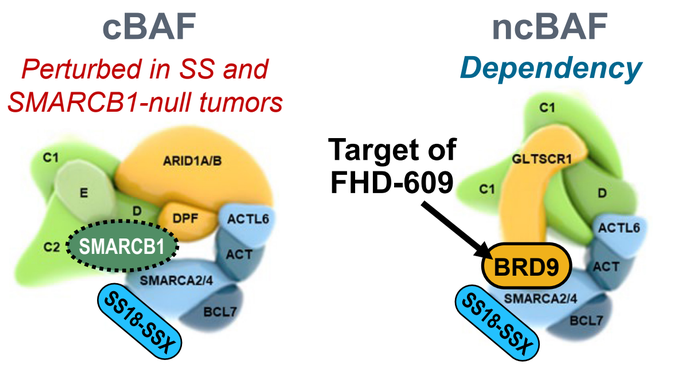
INTRODUCTION

- Bromodomain containing protein 9 (BRD9) is a unique subunit of the noncanonical 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.



- BRD9 represents a selective vulnerability for tumors with certain BAF complex alterations, such as SS18-SSX fusions and SMARCB1 mutations.
- BRD9 has no intrinsic enzymatic activity, necessitating alternative treatment modalities such as targeted protein degradation.

Study FHD-609-C-001 Overview

Study drug administration: FHD-609 administered intravenously twice-weekly (BIW) or once-weekly (QW) in 28-day cycles.

Enrollment: Patients enrolled following a modified 3+3 design.

Key eligibility criteria: Synovial sarcoma or advanced SMARCB1-loss tumor; measurable disease by RECIST v1.1; no other reasonable therapeutic options.

Endpoints: Safety, tolerability, DLTs, and determination of the RP2D(s) as well as PK, preliminary clinical benefit, and PD (BRD9 degradation).

RESULTS

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

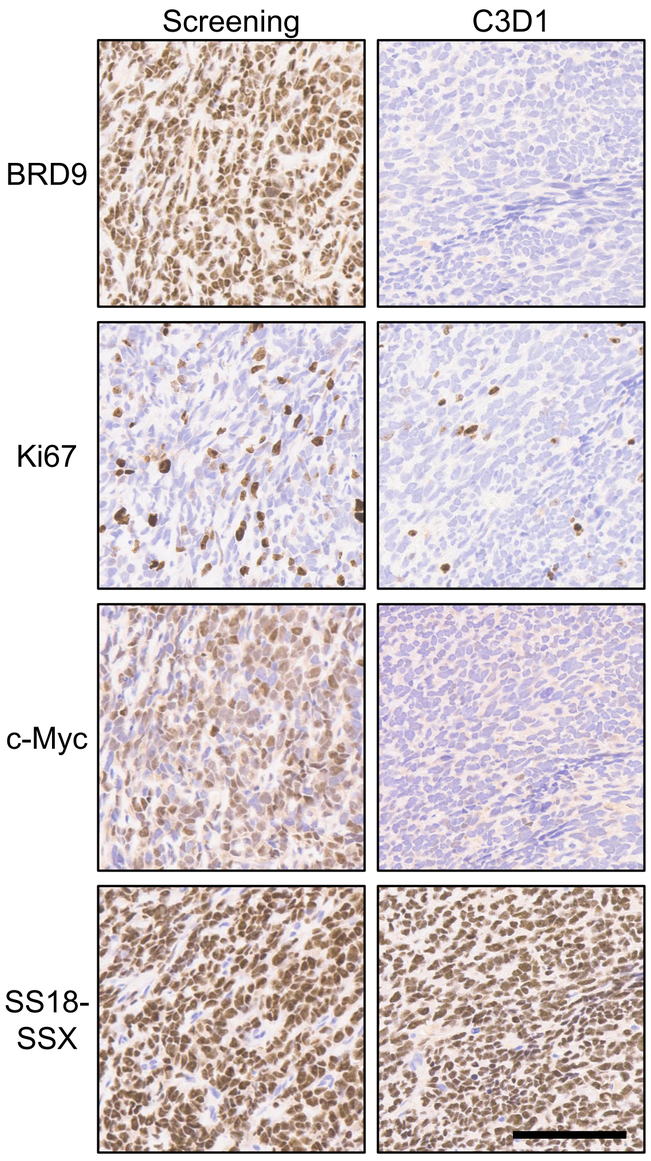


Figure 1. Screening and on-treatment tumor biopsies were analyzed by immunohistochemistry (IHC). Shown are representative images from a subject in the 80 mg BIW dose cohort. Scale bar = 100 µm.

Complete BRD9 degradation observed at ≥ 40 mg BIW

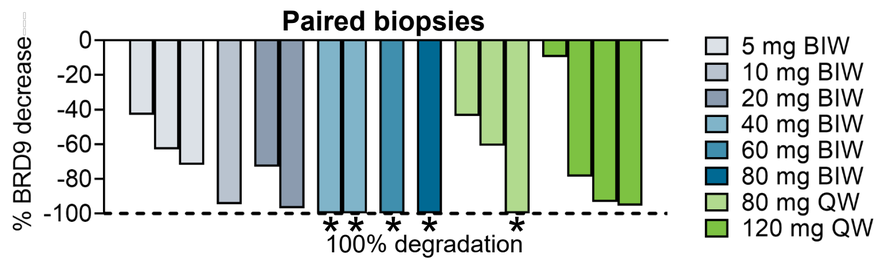


Figure 2. Tumor biopsies were collected at screening and either C2D15, C3D1 or end of treatment (EOT). BRD9 protein levels were scored by a pathologist (H-score). Each bar represents the change in BRD9 H-score relative to screening for an individual patient biopsy.

Dose-dependent duration of BRD9 degradation in peripheral blood and tumor

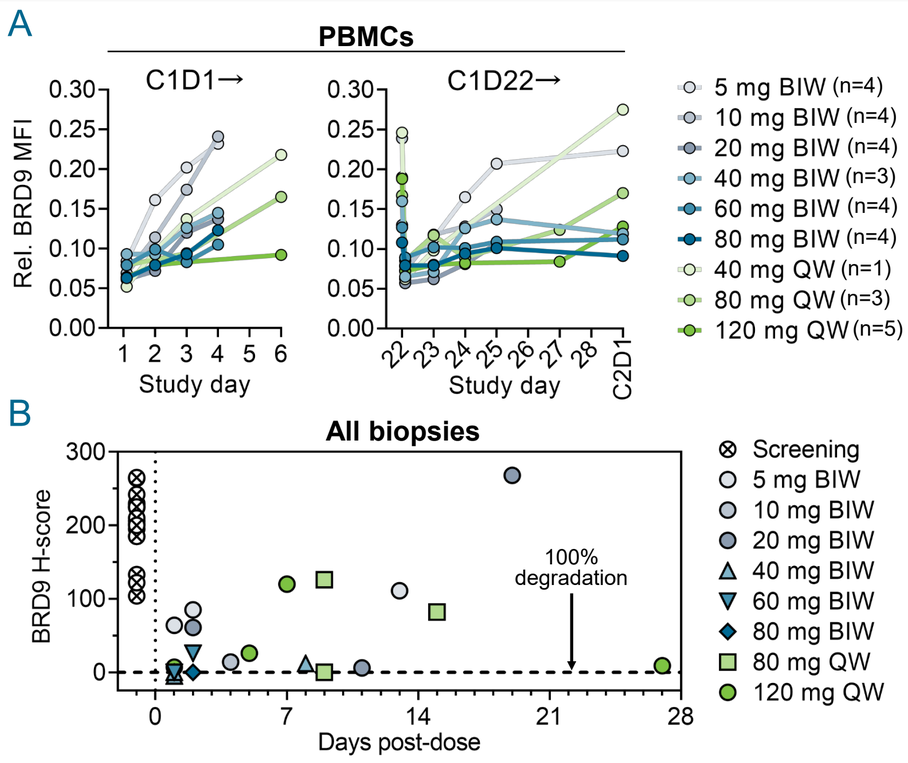


Figure 3. A) BRD9 was analyzed in patient PBMCs by flow cytometry. Shown are plots of the T-cell (CD3+) population, which was found in preclinical studies to be the best tumor surrogate (Ref. 2). Values are mean fluorescence intensity (MFI) relative to each individual patient's C1D1 pretreatment baseline.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

BRD9 degradation associated with reduced markers of proliferation

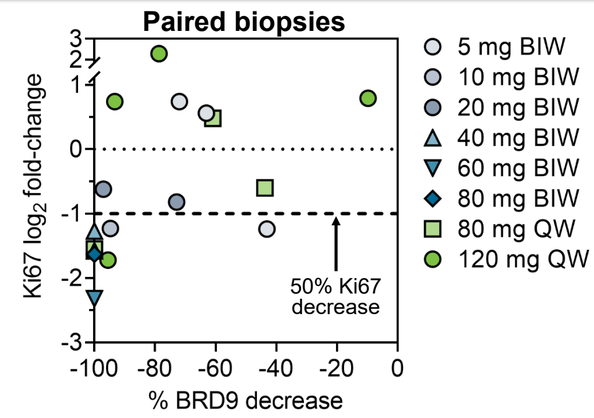


Figure 4. Screening and on-treatment tumor biopsies were scored for Ki67 % positive tumor cells. Each data point represents an individual on-treatment biopsy, with Ki67 and BRD9 changes relative to screening.

Histology changes observed in some cases

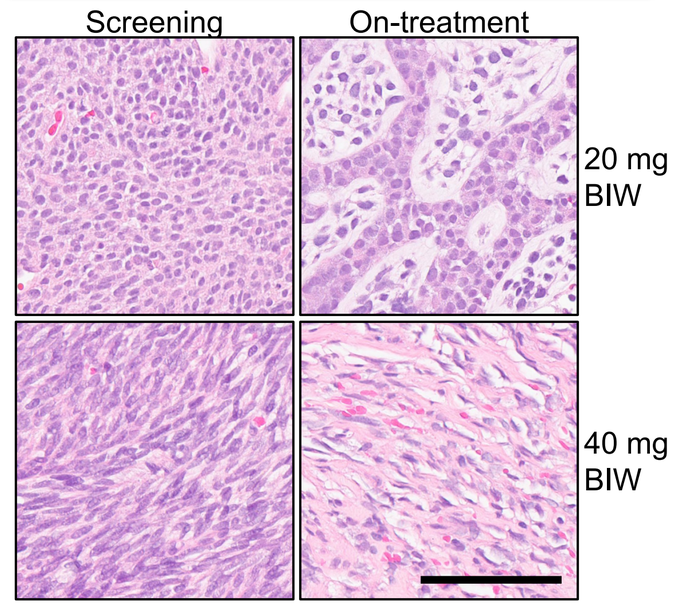
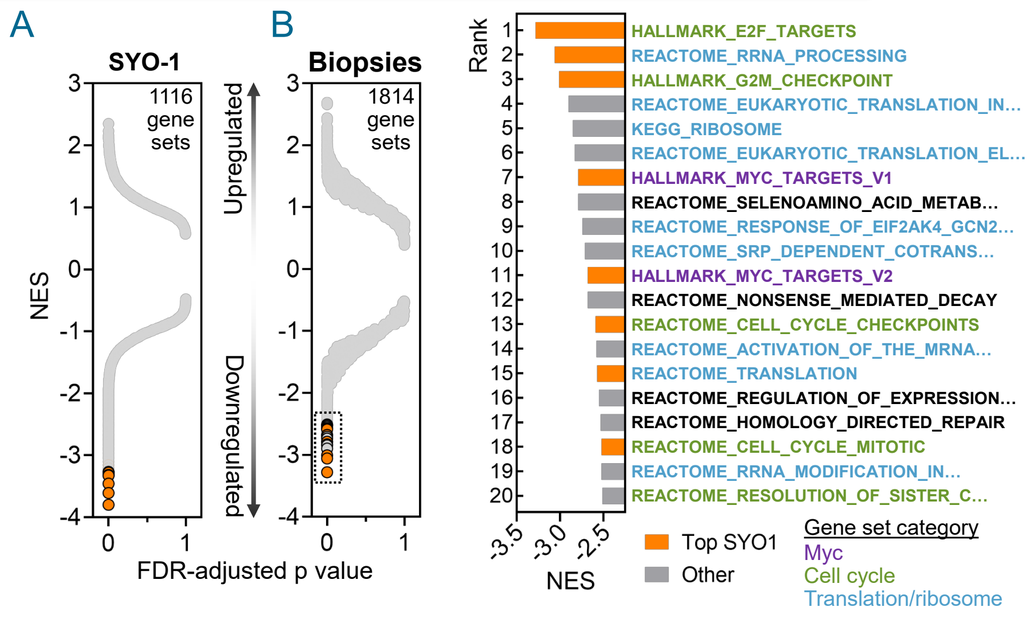


Figure 5. Hematoxylin and eosin staining of paired tumor biopsies. *Top row:* On-treatment biopsy shows fenestrated architecture. *Bottom row:* On-treatment biopsy shows cell dropout and increased collagenous stroma, suggesting decreased tumor density. *Note:* cells with altered morphology retained SS18-SSX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

Downregulation of Myc targets and cell cycle gene sets preclinically and clinically

Figure 6. SYO-1 tumor xenografts and patient biopsies were analyzed by RNA-sequencing. Gene set enrichment analysis (GSEA) was performed, and the Hallmark, KEGG and Reactome gene sets were ranked by normalized enrichment score (NES). **A)** GSEA for mice bearing SYO-1 xenografts treated with either vehicle or 3 mg/kg FHD-609. Highlighted are 8 most strongly downregulated gene sets relative to vehicle control. **B)** GSEA for biopsies from the 40 mg BIW (n=2) and 80 mg BIW (n=1) dose groups. Highlighted are the 20 most strongly downregulated gene sets relative to screening. These include the top 8 preclinical gene sets (orange), as well as other gene sets related to cell growth and proliferation.



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

1. Centore, R. C. *et al. Trends Genet.* **36**, 936–950 (2020)
2. Collins, M. *et al*. CTOS Annual Meeting (2022)
3. Livingston, J. A. *et al.* CTOS Annual Meeting (2023)

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