EVALUATING CLINICAL BIOMARKERS OF FHD-286, A POTENT AND SELECTIVE INHIBITOR OF BRG1/BRM (SMARCA4/2), IN METASTATIC UVEAL MELANOMA

Jessica Wan[1], Kim Horrigan[1], GiNell Elliott[1], Liv Johannessen[1], Mike Collins[1], Alexander J. Lazar[2], Dillon Corrigan[1], Caitlin Patriquin[1], Sam Agresta[1], Jessica Piel[1], Martin Hentemann[1]
[1]Foghorn Therapeutics, Cambridge, MA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX

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ABSTRACT

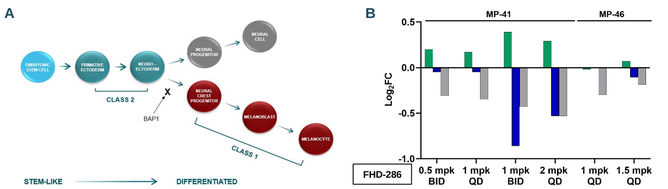
The BRG/Brahma-associated factors (BAF) family of chromatin remodeling complexes (also referred to as the mSWI/SNF complex) regulates chromatin accessibility and gene expression through its ATP-dependent remodeling activity. FHD-286, a first-in-class compound that potently and selectively inhibits the ATPase components of the BAF complex, BRG1 and BRM, was evaluated in a Phase I dose escalation in subjects with metastatic uveal melanoma (mUM) (FHD-286-001). The pharmacodynamics of FHD-286 were assessed to demonstrate proof-of-mechanism and understand the downstream molecular and clinical impact of BRG1/BRM inhibition. In addition, circulating tumor DNA (ctDNA) was evaluated as an early predictor of overall survival benefit.

Seventy-three subjects were on a daily dosing regimen ranging from 2.5 to 10 mg or an intermittent regimen of 1-week on/1-week-off ranging from 10 to 22.5 mg. Tumor biopsies were collected at screening and either Cycle 3, or end of treatment. Biomarker changes in the tumor were observed by histological assessment, by IHC/IF biomarker assays, and RNA sequencing. Observations were suggestive of a differentiation effect by FHD-286 on the tumor cells, including a decrease in stemness genes and an increase in mature melanocytic markers. Evidence of necrosis and a trend of decreasing tumor cell density were also seen. In addition, ctDNA was measured in serial plasma samples using a targeted NGS panel. A reduction in ctDNA was shown in approximately 50% of subjects, which correlated with an increased overall survival benefit. Lastly, serial blood samples collected in Paxgene RNA tubes were analyzed by RNA sequencing. A robust dose-dependent gene signature was identified as a peripheral readout of target engagement at steady-state in both dosing regimens and across dose cohorts.

In summary, we observed changes in the tumor cells at the biopsy site and ctDNA that suggest FHD-286 has a biological impact on uveal melanoma that may lead to clinical benefit. Given the limitations and challenges to obtain tumor biopsies from every subject and at a frequent rate, the identified PD gene signature in the blood is a valuable tool to measure target engagement in this study, and other potential solid tumor indications.

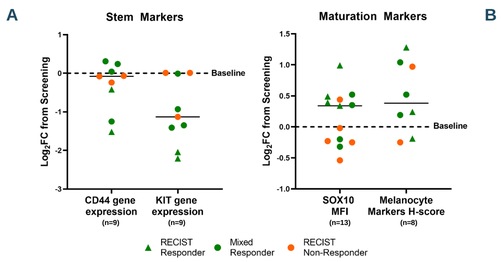
BACKGROUND

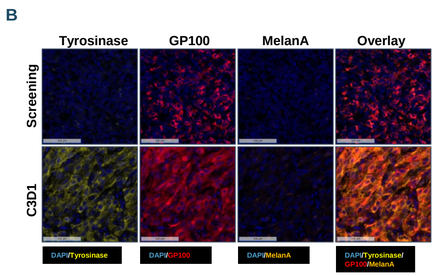
Figure 1. (A) Uveal melanoma can be classified into Class 1 or Class 2 tumors based on the DecisionDx®-UM GEP test, a widely used prognostic test to predict individual risk of metastasis in patients with uveal melanoma[1]. Class 1 and 2 tumors are associated with low and high risk of metastasis, respectively. It has been shown that Class 2 tumors are less differentiated due to being stuck in a more stem-like state[2] (Figure adapted from paper). **(B)** We have previously shown that treatment with FHD-286 in two uveal melanoma preclinical models results in a positive shift in the GEP genes and PRAME, another marker of poor prognosis, by RNA-seq[3].



RESULTS

FHD-286 treatment has a favorable impact on stem and maturation markers, which is more profound in subjects with a tumor response





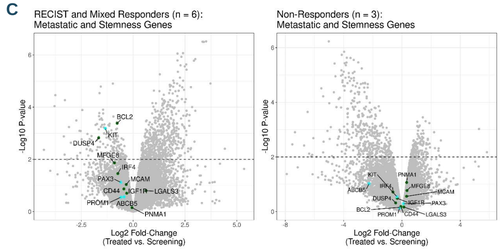
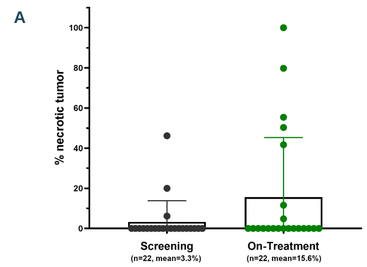
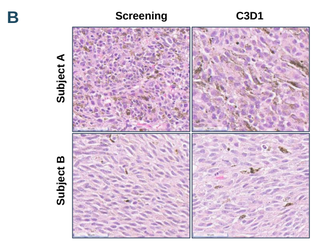
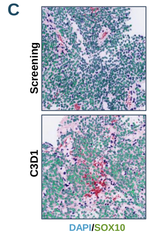


Figure 2. Paired tumor biopsies from up to thirteen subjects were analyzed for protein changes by immunofluorescence (IF) staining and gene expression changes by RNA-seq. **(A)** Mean Log_2FC from screening is annotated. Melanocyte Markers H-score is a composite score from 3 melanocyte markers – Tyrosinase, GP100, and MelanA. Subjects were classified as a mixed responder if they had a stable disease (SD) target lesion response but not an overall RECIST response. **(B)** Example images of the melanocyte multiplex IF panel on a tumor biopsy pair. The baseline expression of each melanocyte marker varies across subjects (data not shown). H-scores for individual marker were quantified using image analysis. The average Log2FC from screening is plotted in (A). **(C)** Differential gene expression in the RECIST and mixed responders vs. RECIST non-responders. Markers associated with metastatic uveal melanoma[4] (green) and general markers associated with pluripotency or stemness (cyan) are annotated.

Evidence of necrosis and lower tumor cell density were seen in on-treatment biopsies







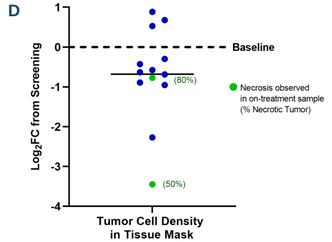
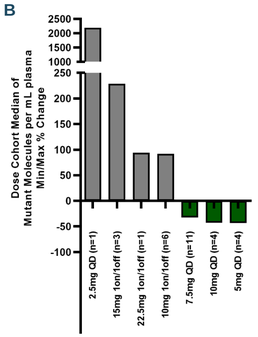


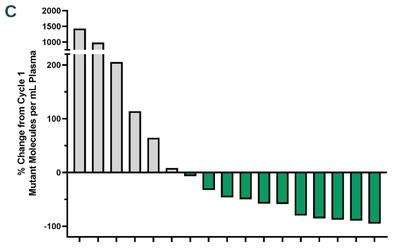
Figure 1. (A) Viable and necrotic tumor areas were annotated in H&E images on paired tumor biopsies from 22 subjects. % necrotic tumor was estimated based on these areas. 1 of 22 subjects had necrosis in the screening and on-treatment sample. Mean with SD is annotated. **(B)** Example H&E images from two tumor biopsy pairs. Cells were observed to be less densely packed in the on-treatment samples than in the screening samples. **(C)** Example images of SOX10 IF staining in a tumor biopsy pair. **(D)** Tumor cell density, defined as the number of tumor cells (SOX10+) per area of total tissue in mm^2, was quantified using image analysis. The median density across ROIs per sample was calculated and normalized to screening. Mean Log2FC from screening is annotated.

FHD-286 demonstrates reduction in ctDNA, which correlates with apparent survival benefit

A

# of Subjects	#	%
Analyzed	36	
Fully Evaluable	29	
With ctDNA reduction >90%	4	14
With any ctDNA reduction from Cycle 1 (by 9 weeks)	**15**	**52**





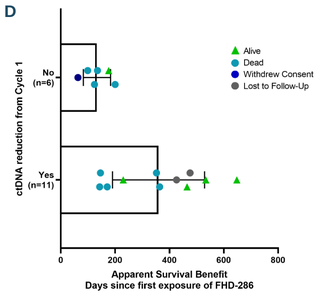
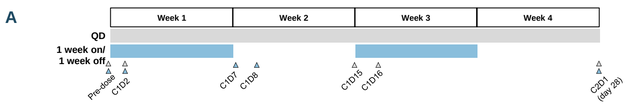


Figure 4. (A) Circulating tumor DNA (ctDNA) analysis table summary. ctDNA was measured by a targeted NGS panel in serial blood samples. ctDNA levels were quantified as mutant molecules per mL of plasma. **(B)** The % change from the minimum and maximum ctDNA levels was calculated for each subject. The median of each cohort is shown. **(C)** Change in ctDNA from Cycle 1 for individual subjects in the 5mg, 7.5mg, and 10mg QD cohorts who were on FHD-286 for at least one cycle (n=17). **(D)** Comparing the apparent survival benefit between subjects in (C) where a reduction in ctDNA from Cycle 1 was seen or not. Mean with SD is annotated. Apparent survival benefit is in the context of subjects going on additional therapies after coming off study for FHD-286. Survival is based on the known date of death or last survival follow-up, with a data cut-off of July 24, 2023. Survival times are subject to change as future information is collected.

Robust blood PD signature can be used as a peripheral readout of FHD-286 target engagement



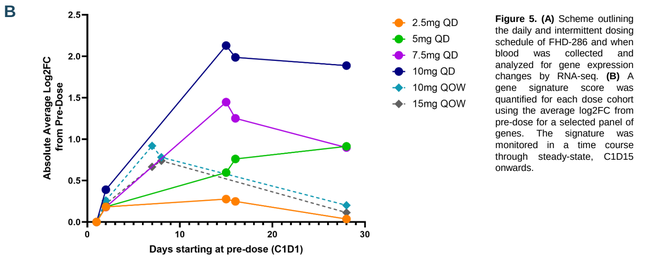
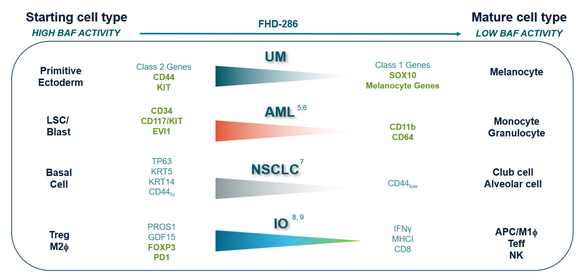


Figure 5. (A) Scheme outlining the daily and intermittent dosing schedule of FHD-286 and when blood was collected and analyzed for gene expression changes by RNA-seq. **(B)** A gene signature score was quantified for each dose cohort using the average log2FC from pre-dose for a selected panel of genes. The signature was monitored in a time course through steady-state, C1D15 onwards.

CONCLUSIONS

- We have evaluated the biological impact of FHD-286, a first-in-class, selective, oral allosteric inhibitor of BRM/BRG1, in patients with metastatic uveal melanoma.
- Changes we observed suggest FHD-286 may lead to loss of stem-like properties and a broader impact on the tumor cellular architecture that may be not captured by RECIST criteria.
- We showed that reduction in ctDNA can be used as surrogate for improved patient survival benefit.
- Lastly, we identified a blood gene signature that can be used to monitor target engagement of FHD-286 in potential future clinical studies. Target engagement was not sustained during the off-week in the intermittent dose cohorts.
- We propose that FHD-286 is a broad differentiation agent that can suppress stem-like transcriptional programs across a wide range of mutational and lineage backgrounds.



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