A Phase 1 Dose Escalation and Expansion Study of FHD-286, a Novel BRG1/BRM (SMARCA4/SMARCA2) Inhibitor, for the Treatment of Metastatic Uveal Melanoma

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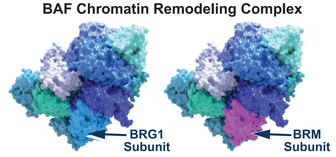
Background: FHD-286

FHD-286 is a first-in-class, orally administered compound that potently and selectively inhibits the ATPase components of the BAF complex.

- FHD-286 is a potent, selective, allosteric, and orally available small molecule inhibitor of the enzymatic activity of BRG1/BRM (SMARCA4/2).
- BRG1 and BRM are the catalytic core of a subset of chromatin remodeling complexes known as BAF (BRG1/Brahma-associated factor) complexes.
- BAF complexes are critical to the regulation of cellular differentiation and proliferation: mutations in BAF are implicated in cancer as well as other diseases.

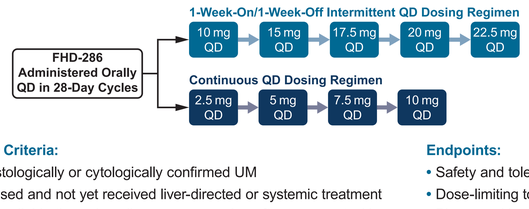
BAF Chromatin Remodeling Complex



Phase 1 International, Multicenter, Open-Label Study (NCT04879017)

FHD-286 is administered orally in patients with metastatic uveal melanoma (UM).

Study FHD-286-C-001 Dose Escalation Phase



Key Eligibility Criteria:

- Metastatic histologically or cytologically confirmed UM
- Newly diagnosed and not yet received liver-directed or systemic treatment
- Ineligible for available therapies, disease progression after treatment with available therapies, and/or intolerant to available therapies

Endpoints:

- Safety and tolerability
- Dose-limiting toxicities (DLTs)
- Pharmacokinetics (PK)
- Preliminary clinical activity

Baseline Demographics and Disease Characteristics

Baseline characteristics were generally well balanced across all doses.

Parameter		Continuous QD Dosing Regimen				1-Week-On/1-Week-Off Intermittent QD Dosing Regimen					All Doses
		2.5 mg (N=2)	5 mg (N=12)	7.5 mg (N=17)	10 mg (N=9)	10 mg (N=10)	15 mg (N=9)	17.5 mg (N=3)	20 mg (N=5)	22.5 mg (N=6)	Total (N=73)
Age (years)	Median (min, max)	63.5 (59, 68)	72.5 (47, 79)	61 (42, 75)	63 (52, 81)	70.5 (50, 77)	65 (40, 81)	69 (63, 78)	62 (43, 78)	68 (61, 73)	65 (40, 81)
Gender, n (%)	Male	1 (50)	7 (58.3)	7 (41.2)	6 (66.7)	6 (60)	5 (55.6)	0	3 (60)	3 (50)	38 (52.1)
	Female	1 (50)	5 (41.7)	10 (58.8)	3 (33.3)	4 (40)	4 (44.4)	3 (100)	2 (40)	3 (50)	35 (47.9)
Race, n (%)	White	2 (100)	12 (100)	13 (76.5)	9 (100)	7 (70)	5 (55.6)	1 (33.3)	5 (100)	3 (50)	57 (78.1)
	Not Reported	0	0	4 (23.5)	0	3 (30)	4 (44.4)	2 (66.7)	0	3 (50)	16 (21.9)
ECOG PS	0	1 (50)	4 (33.3)	8 (47.1)	5 (55.6)	5 (50)	5 (55.6)	3 (100)	3 (60)	4 (66.7)	38 (52.1)
	1	1 (50)	7 (58.3)	8 (47.1)	4 (44.4)	5 (50)	4 (44.4)	0	2 (40)	2 (33.3)	33 (45.2)
	2	0	1 (8.3)	1 (5.9)	0	0	0	0	0	0	2 (2.7)
Time Since Metastatic Cancer Diagnosis (years)	n (%)	2 (100)	12 (100)	17 (100)	9 (100)	10 (100)	8 (88.9)	3 (100)	4 (80)	6 (100)	71 (97.3)
	Median (min, max)	2.6 (2.5, 2.8)	1.4 (0.2, 4.1)	1.5 (0.7, 4.8)	1.5 (0.3, 6)	1.5 (0.2, 7.6)	1.5 (0.2, 20.1)	3.3 (1.7, 8)	1.9 (0.2, 3.1)	2.4 (1.6, 4.4)	1.7 (0.2, 20.1)
Liver Metastasis, n (%)	Yes	2 (100)	12 (100)	13 (76.5)	9 (100)	10 (100)	7 (77.8)	3 (100)	5 (100)	6 (100)	67 (91.8)
	No	0	0	4 (23.5)	0	0	2 (22.2)	0	0	0	6 (8.2)
Number of Prior Lines of Chemotherapy/ Immunotherapy	n (%)	2 (100)	11 (91.7)	17 (100)	8 (88.9)	8 (80)	8 (88.9)	3 (100)	5 (100)	6 (100)	68 (93.2)[a]
	Median (min, max)	2.5 (1, 4)	2 (1, 6)	2 (1, 6)	2 (1, 5)	2 (2, 6)	2 (1, 4)	3 (1, 3)	2 (1, 6)	3 (3, 4)	2 (1, 6)

Data cutoff date 24 July 2023. [a]All patients had prior anticancer therapy including surgery, radiotherapy, and/or chemotherapy/immunotherapy; 64% of patients had prior surgery and 80% of patients had prior radiotherapy.

Patient Disposition

Parameter	Continuous QD Dosing				1-Week-On/1-Week-Off Intermittent QD Dosing Regimen					All Doses
	2.5 mg (N=2)	5 mg (N=12)	7.5 mg (N=17)	10 mg (N=9)	10 mg (N=10)	15 mg (N=9)	17.5 mg (N=3)	20 mg (N=5)	22.5 mg (N=6)	Total (N=73)
Patients Dosed	2 (100)	12 (100	17 (100)	9 (100)	10 (100)	9 (100)	3 (100)	5 (100)	6 (100)	73 (100)
Patients Who Were Ongoing on Study Treatment	0	0	0	0	0	1 (11.1)	2 (66.7)	0	1 (16.7)	4 (5.5)
Patients Who Discontinued Study Treatment	2 (100)	12 (100)	17 (100)	9 (100)	10 (100)	8 (88.9)	1 (33.3)	5 (100)	5 (83.3)	69 (94.5)
Reason for Discontinuation of Study Treatment										
Disease Progression/Treatment Failure	2 (100)	6 (50)	10 (58.8)	5 (55.6)	6 (60)	7 (77.8)	1 (33.3)	2 (40)	3 (50)	42 (57.5)
Clinical Suspicion of Disease Progression	0	4 (33.3)	3 (17.6)	2 (22.2)	2 (20)	0	0	0	1 (16.7)	12 (16.4)
Withdrawal of Consent	0	0	3 (17.6)	0	0	1 (11.1)	0	1 (20)	0	5 (6.8)
Adverse Event	0	1 (8.3)	0	0	1 (10)	0	0	2 (40)	0	4 (5.5)
Other	0	1 (8.3)	0	1 (11.1)	0	0	0	0	1 (16.7)	3 (4.1)
Death	0	0	0	1 (11.1)	1 (10)	0	0	0	0	2 (2.7)
PI Decision	0	0	1 (5.9)	0	0	0	0	0	0	1 (1.4)

Data cutoff date 24 July 2023.

Abbreviations: 1O1F = 1 week on/1-week off intermittent daily dosing; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATPase = adenosine triphosphatase; ECOG = Eastern Cooperative Oncology Group; NGS = next-generation sequencing; PS = performance status; PI = principal investigator; QD = once daily.

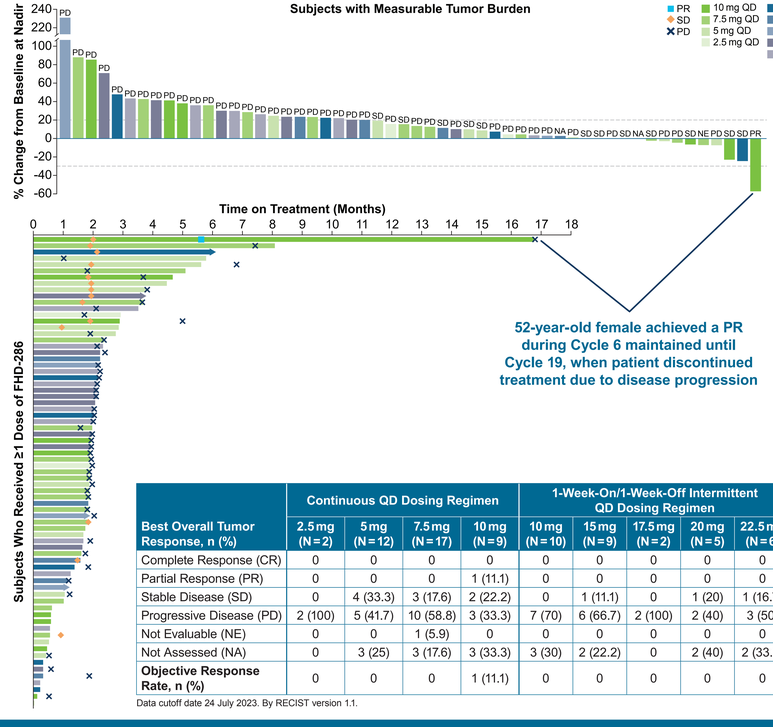
Disclosures: Sapna P. Patel DOI: Institutional clinical trial support: Bristol Myers Squibb, Foghorn Therapeutics, Ideaya, InxMed, Lyvgen, Novartis, Provectus Biopharmaceuticals, Seagen, Syntrix Bio, TriSalus Life Sciences; Advisory board, steering committee, data safety monitoring board, consulting: Advance Knowledge in Healthcare*, Bristol Myers Squibb, Cardinal Health*, Castle Biosciences, Clinical Care Options, Delcath*, Immatics*, Immunocore*, Medscape, MSD, Novartis*, OncoSec*, Pfizer*, Replimune, Total CME, TriSalus Life Sciences; Speakers fees (non-promotional): MSD; Note: *completed. Contact: SPPatel@mdanderson.org.

Summary of Treatment-Related AEs (TRAEs) and Dose-Limiting Toxicities by Dose Cohort

Parameter	Continuous QD Dosing Regimen				1-Week-On/1-Week-Off Intermittent QD Dosing Regimen					All Doses
	2.5 mg (N=2)	5 mg (N=12)	7.5 mg (N=17)	10 mg (N=9)	10 mg (N=10)	15 mg (N=9)	17.5 mg (N=3)	20 mg (N=5)	22.5 mg (N=6)	Total (N=73)
Any TRAE, n (%)	2 (100)	9 (75.0)	15 (88.2)	8 (88.9)	8 (80.0)	9 (100)	3 (100)	5 (100)	6 (100)	65 (89)
Clinical Adverse Events (≥15%)										
Dysgeusia	0	5 (41.7)	12 (70.6)	3 (33.3)	3 (30)	3 (33.3)	2 (66.7)	2 (40)	4 (66.7)	34 (46.6)
Fatigue	2 (100)	4 (33.3)	6 (35.3)	4 (44.4)	2 (20)	4 (44.4)	1 (33.3)	5 (100)	0	28 (38.4)
Nausea/Vomiting[a]	1 (50)	3 (25)	7 (41.2)	4 (44.4)	4 (40)	4 (44.4)	1 (33.3)	2 (40)	2 (33.3)	28 (38.4)
Rash[b]	1 (50)	0	5 (29.4)	4 (44.4)	3 (30)	6 (66.7)	1 (33.3)	2 (40)	3 (50)	25 (34.2)
Decreased appetite	0	3 (25)	6 (35.3)	3 (33.3)	2 (20)	4 (44.4)	2 (66.7)	2 (40)	2 (33.3)	24 (32.9)
Dry mouth	0	5 (41.7)	5 (29.4)	3 (33.3)	2 (20)	0	2 (66.7)	3 (60)	3 (50)	23 (31.5)
Pruritus	0	1 (8.3)	3 (17.6)	1 (11.1)	3 (30)	1 (11.1)	1 (33.3)	1 (20)	4 (66.7)	15 (20.5)
Alopecia	0	2 (16.7)	1 (5.9)	2 (22.2)	1 (10)	1 (11.1)	0	4 (80)	3 (50)	14 (19.2)
Diarrhoea	1 (50)	3 (25)	1 (5.9)	0	2 (20)	3 (33.3)	0	1 (20)	2 (33.3)	13 (17.8)
Laboratory Adverse Events (≥15%)										
AST increased	0	4 (33.3)	3 (17.6)	3 (33.3)	4 (40)	2 (22.2)	1 (33.3)	1 (20)	1 (16.7)	19 (26)
Decreased platelet count[c]	0	1 (8.3)	1 (5.9)	4 (44.4)	1 (10)	2 (22.2)	1 (33.3)	2 (40)	4 (66.7)	16 (21.9)
ALT increased	0	3 (25)	2 (11.8)	3 (33.3)	1 (10)	2 (22.2)	1 (33.3)	2 (40)	1 (16.7)	15 (20.5)
Troponin increased[d]	0	2 (16.7)	1 (5.9)	2 (22.2)	1 (10)	3 (33.3)	0	3 (60)	0	12 (16.4)
Any Serious TRAE	0	1 (8.3)	1 (5.9)	2 (22.2)	1 (10)	0	0	0	1 (16.7)	6 (8.2)
Any TRAE leading to dose reduction	0	0	1 (5.9)	2 (22.2)	0	0	0	0	2 (33.3)	5 (6.8)
Any TRAE leading to dose interruption	1 (50)	3 (25)	6 (35.3)	5 (55.6)	0	3 (33.3)	0	5 (100)	4 (66.7)	27 (37)
Dose-Limiting Toxicities										
Keratitis	0	0	1 (5.9)	0	0	0	0	0	0	1 (1.4)
Muscular weakness	0	0	0	0	0	0	0	1 (20)	0	1 (1.4)
Platelet count decreased	0	0	0	0	0	0	0	0	1 (16.7)	1 (1.4)
Rash[e]	0	0	0	0	0	0	0	0	1 (16.7)	1 (1.4)

Data cutoff date 24 July 2023. [a]Nausea/Vomiting includes PTs of nausea, vomiting, retching. [b]Rash includes PTs of acute febrile neutrophilic dermatosis, drug eruption, skin erosion, skin exfoliation, exfoliative rash, rash macular, dermatitis allergic, dermatitis bullous, rash erythematous, rash generalized, urticaria, rash maculo-papular, rash, rash papular, rash pruritic, rash pustular, rash vesicular, butterfly rash. [c]Decreased platelet count includes PTs of thrombocytopenia, platelet count decreased. [d]Troponin increased includes PTs of troponin increased, troponin I increased, and troponin T increased. [e]2 patients enrolled after the clearance of the dose level occurred experienced DLTs of Grade 3 Rash on the 7.5 mg QD continuous dosing regimen (at Day 18 and Day 23).

Efficacy: Tumor Response

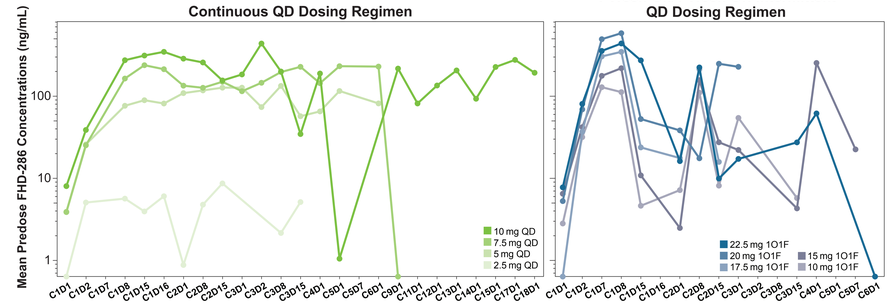


Best Overall Tumor Response, n (%)	Continuous QD Dosing Regimen				1-Week-On/1-Week-Off Intermittent QD Dosing Regimen					All Doses
	2.5 mg (N=2)	5 mg (N=12)	7.5 mg (N=17)	10 mg (N=9)	10 mg (N=10)	15 mg (N=9)	17.5 mg (N=2)	20 mg (N=5)	22.5 mg (N=6)	Total (N=72)
Complete Response (CR)	0	0	0	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	1 (11.1)	0	0	0	0	0	1 (1.4)
Stable Disease (SD)	0	4 (33.3)	3 (17.6)	2 (22.2)	0	1 (11.1)	0	1 (20)	1 (16.7)	12 (16.7)
Progressive Disease (PD)	2 (100)	5 (41.7)	10 (58.8)	3 (33.3)	7 (70)	6 (66.7)	2 (100)	2 (40)	3 (50)	40 (55.6)
Not Evaluable (NE)	0	0	1 (5.9)	0	0	0	0	0	0	1 (1.4)
Not Assessed (NA)	0	3 (25)	3 (17.6)	3 (33.3)	3 (30)	2 (22.2)	0	2 (40)	2 (33.3)	18 (25)
Objective Response Rate, n (%)	0	0	0	1 (11.1)	0	0	0	0	0	1 (1.4)

Data cutoff date 24 July 2023. By RECIST version 1.1.

Plasma Pharmacokinetics: Mean Predose PK Profiles

- FHD-286 exposure increases with dose between 2.5 mg QD and 10 mg QD and accumulates with QD dosing; steady state typically reached by 2 weeks
- FHD-286 half-life is >24 hours



Preliminary Data from Circulating Tumor DNA (ctDNA) Analysis

Observed reduction in ctDNA levels with FHD-286 may lead to longer apparent survival benefit.

(A) ctDNA analysis summary. ctDNA was measured by a targeted NGS panel in serial blood samples and 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 patient. The median of each cohort is shown. (C) Change in ctDNA from Cycle 1 for individual patients in the 5 mg, 7.5 mg, and 10 mg QD cohorts who were on FHD-286 for at least one cycle (n=17). (D) Comparing the apparent survival benefit between patients in (C) where a reduction in ctDNA from Cycle 1 was seen or not. Mean ± SD is annotated. Apparent survival benefit is in the context of patients 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 cutoff of 24 July 2023. Survival times are subject to change as future information is collected.

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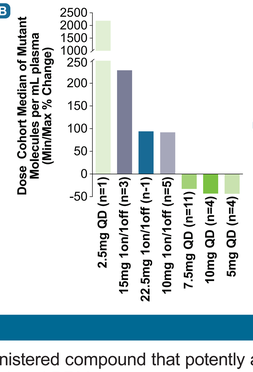
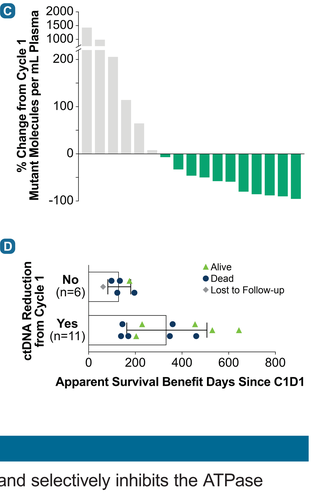
# of Patients	#	%
Analyzed	36	
Fully Evaluable	29	
With ctDNA reduction >90%	4	14
With any ctDNA reduction from Cycle 1 (by 9 weeks)	**15**	**52**





Conclusions

- FHD-286 is a first-in-class, orally administered compound that potently and selectively inhibits the ATPase components of the BAF complex, BRG1 and BRM.
- FHD-286 has been generally well tolerated at continuous daily dose levels of up to 7.5 mg QD, and at intermittent dose levels of up to 17.5 mg QD.
  - » 1 patient treated at the 7.5 mg QD continuous dose level experienced a DLT of Grade 3 keratitis.
    - 2 patients enrolled to this dose level after it was cleared experienced DLTs of Grade 3 rash.
  - » 1 patient treated at the 20 mg QD 1-week-on/1-week-off dose level experienced a DLT of Grade 3 muscular weakness
  - » 2 patients treated at the 22.5 mg QD 1-week-on/1-week-off dose level experienced DLTs: Grade 3 platelet count decreased, which progressed to Grade 4, and Grade 3 rash.
- FHD-286 exposure increased with doses between 2.5 mg QD and 10 mg QD; FHD-286 accumulates with QD dosing, with steady state typically reached by 2 weeks.
- At the data cutoff, 12 patients achieved a best overall response of stable disease with 9 patients showing observed reductions in tumor burden. One patient initially treated at the 10 mg QD dose level achieved a partial remission and showed a 57% decrease in tumor burden.

Acknowledgements: We would like to formally thank the patients, families, co-investigators, and all study personnel for their contributions and participation in the trial. Study sponsored by Foghorn Therapeutics Inc.