# Disclosure Information

## AACR NDOH

## Murphy Hentemann

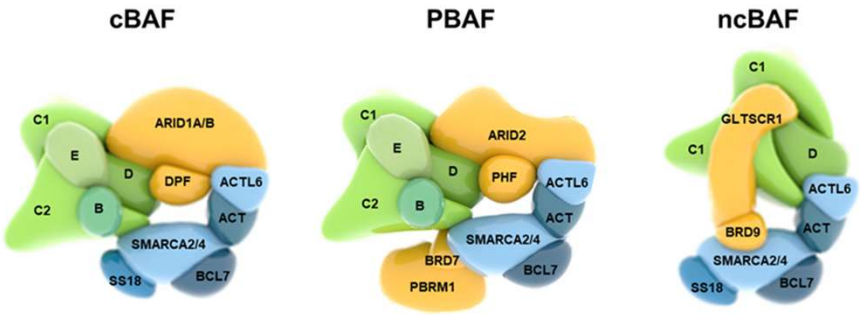
**I have the following relevant financial relationships to disclose:**

**I am an employee and shareholder of Foghorn Therapeutics**


# Pharmacological profile and anti-tumor properties of FHD-286, a novel BAF inhibitor for the treatment of transcription factor-driven cancers

Murphy Hentemann, on behalf of the FHD-286 team
April 2022

# BAF complex dysregulation drives oncogenic transcription



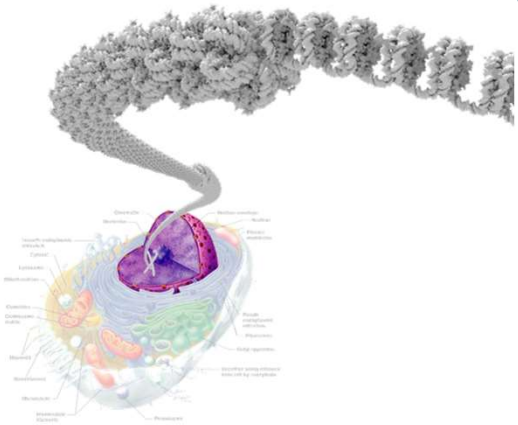

- BAF complexes are critical regulators of chromatin structure and gene expression
- Over 20% of all human cancers harbor a mutation in at least one BAF complex subunit
- Foghorn's unique platform produces full BAF complexes and transcription factors

**We are exploring the enzymatic inhibition of BAF ATPases, SMARCA2 and SMARCA4 (BRM/BRG1)**

# The Chromatin Regulatory System Orchestrates Gene Expression

Two Major Components Work in Concert - Chromatin Remodeling Complexes and Transcription Factors

**Chromatin**

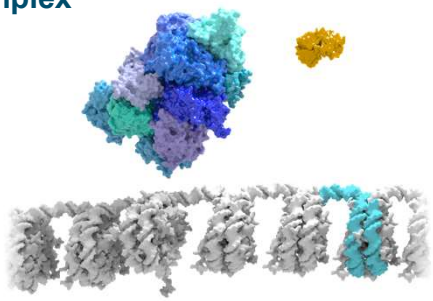


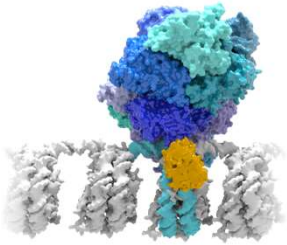
**Chromatin – compacted form of DNA inside the nucleus of the cell**

**1** **Work together to orchestrate gene expression**

**Chromatin remodeling complex**

**Transcription Factor**

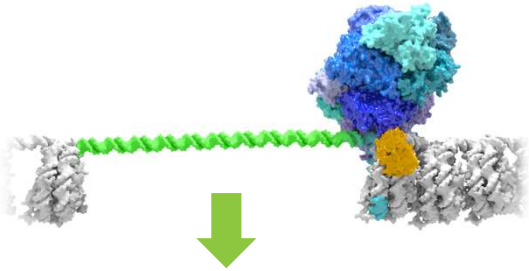




**Right genes**

**2** **TF's guide chromatin remodeling complexes to the right locations**

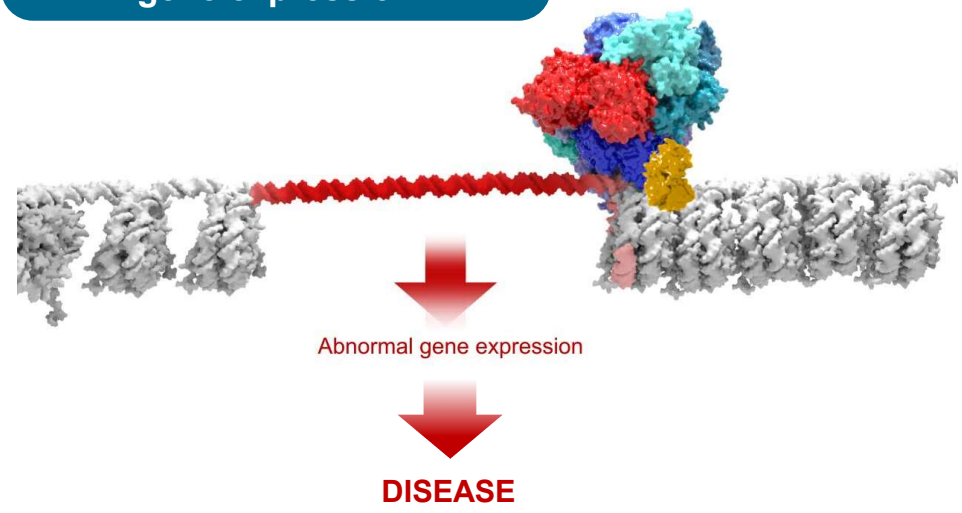
**3** **Once chromatin unpacked, gene expression can occur**



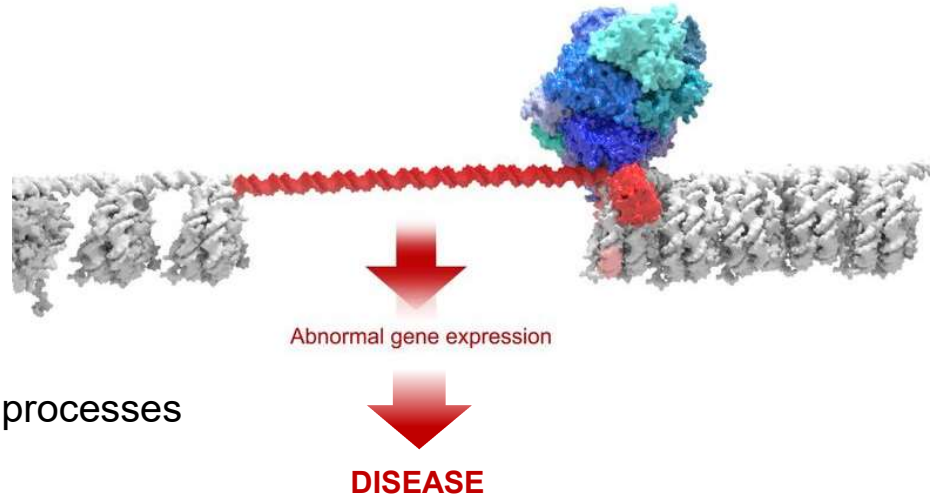
**Normal gene expression**

# Breakdowns in the Chromatin Regulatory System Lead to Disease

**Mutations or overexpression in chromatin remodeling complexes result in abnormal gene expression**

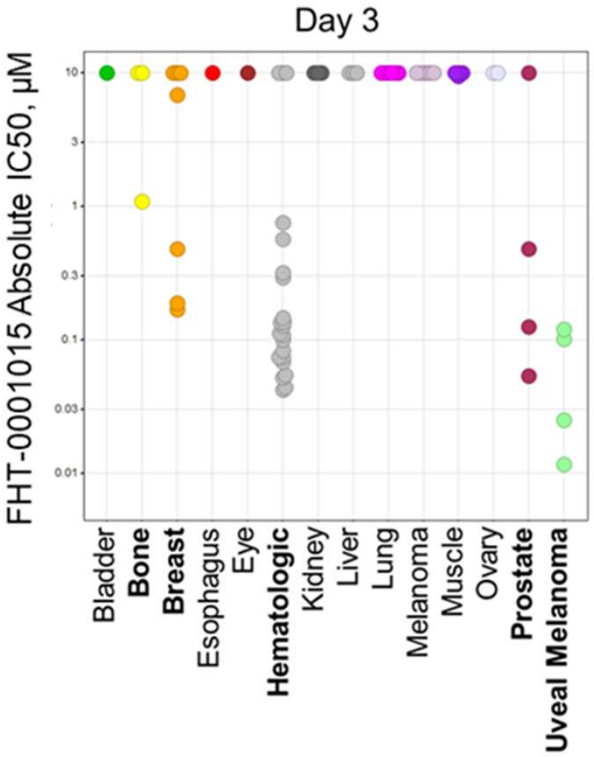


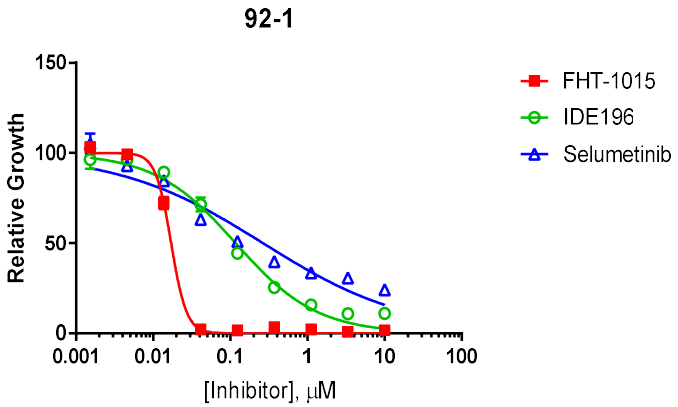

**Mutated or overexpressed TF hijacks chromatin remodeling complex to wrong location**



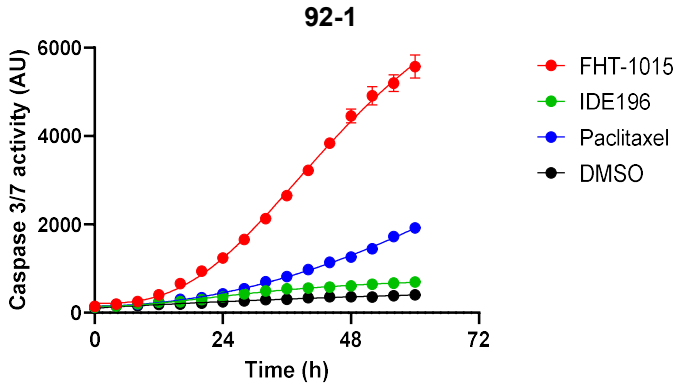

Targeting BRM/BRG1 should block both of these disease processes

# Uveal melanoma cell lines are exquisitely sensitive to BRM/BRG1 inhibition




**Growth Inhibition**




**Caspase 3/7 activity**

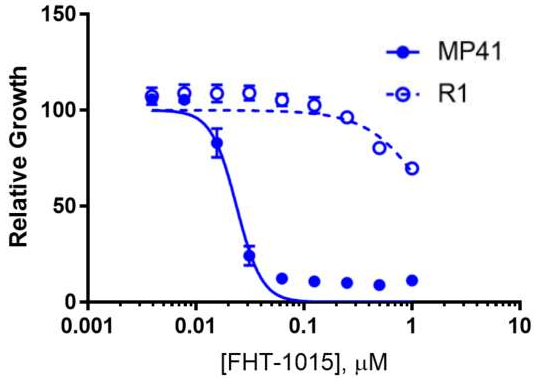
Additional lines show similar sensitivity after 10 days of incubation

# Resistance studies demonstrate that observed activity is on target

MP41 UM cell line

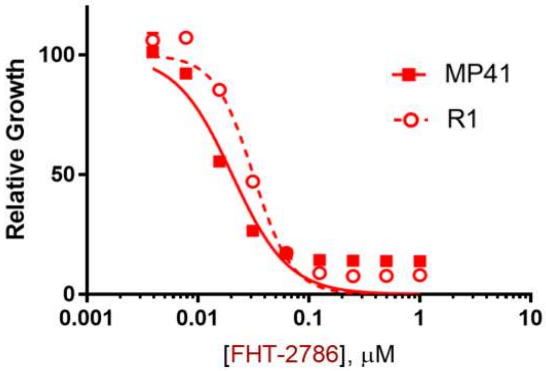
FHT-1015 @ IC90

~ 3 months



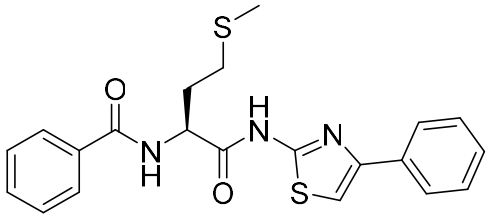

BRG1 I1173->M

FHT-2786 binds to a different pocket in BRG1



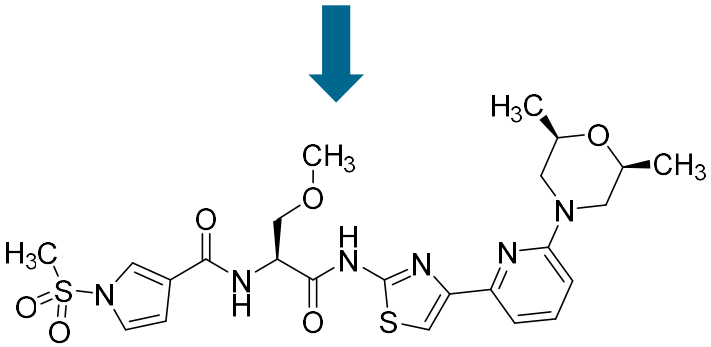

- These data confirm that the anti-proliferative impact of Foghorn compounds is an on-target event
- Understanding of our binding mode enabled a structure-based chemistry approach
- FHD-286 binds in a different site from other literature compounds

# FHD-286 has been identified as our clinical candidate



BRG1: 10 μM
BRM: 10 μM

Screening hit FHT-215



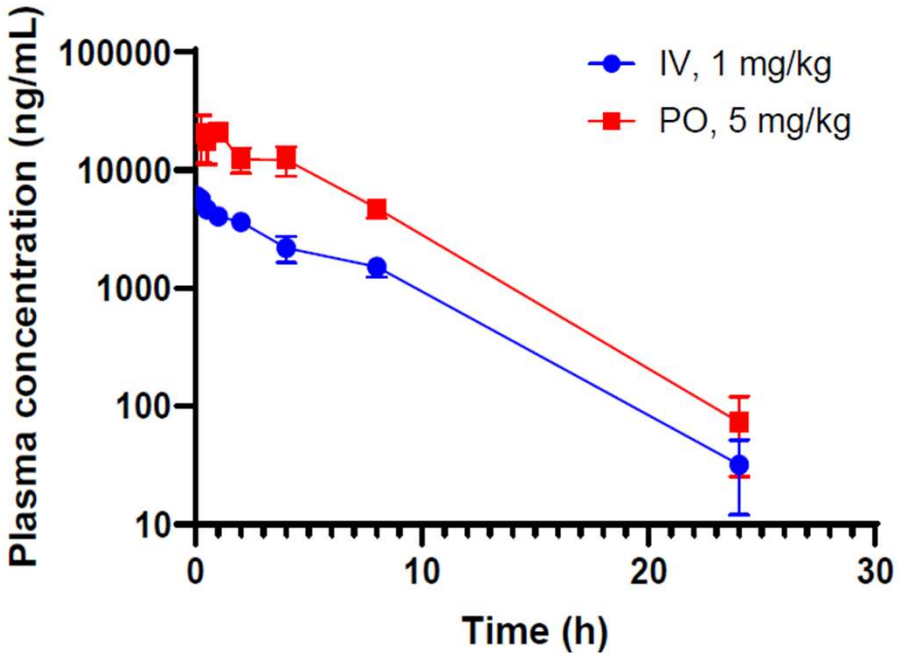
FHD-286

| Category | Criteria | FHD-286 |
|---|---|---|
| *in vitro* profile | • BRG-1 ($IC_{50}$ <0.050 μM)<br>• BRM ($IC_{50}$ <0.050 μM) | 0.006 μM<br>0.005 μM |
| | • MDA-MMTV ($IC_{50}$ <0.050 μM) | 0.010 μM |
| | • 92-1 Cell Viability ($GI_{50}$ <0.050 μM) | <0.001 μM |
| | • SBC5 (10d assay general cell viability $GI_{50}$ >25 μM) | >25 μM |
| ADME / PK Properties | • Solubility [>10 μM for FaSSIF] | 136 μM |
| | • Medium to low CL in human microsomes [HLM <30 μg/min/mg] | 27.9 |
| | • *in vivo* PK: low dose oral F >20% BA in mouse, rat, dog, cyno to support bid or qd dosing<br>• Dose proportionality in rodents | %F<br>~100% (Rat)<br>~100% (Dog)<br>51.1% (Cyno) |
| In-vitro and in-vivo safety | • hERG (patch clamp $IC_{50}$ > 10 μM) | >30 μM |
| | • CYP $IC_{50}$ > 10 μM (across isoforms)<br>• No PXR / No CYP3A4 TDI | Clean, 2C9 ($IC_{50}$ ~10.9 μM) |
| | • Acceptable Eurofins SAFETYscan (Safety47 panel) [$IC_{50}$ >10 μM] | Clean; [$IC_{50}$ >10 μM] Achieved |
| | • ATPase Panel [$IC_{50}$ >10 μM]<br>• Kinome Scan | Clean |

FHD-286 is a highly potent, selective, oral, first in class inhibitor of BRM/BRG1

# FHD-286 has good oral bioavailability and low clearance

*FHD-286 Concentration-time profile in mouse*

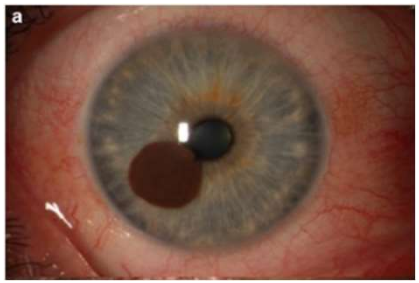


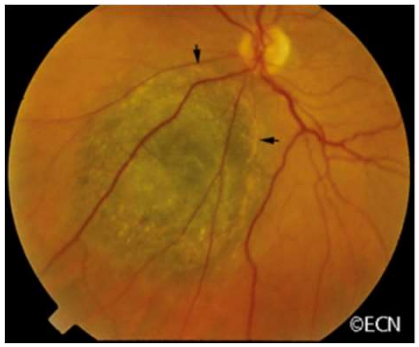

- FHD-286 showed low clearance in nonclinical species
- Good oral bioavailability of suspension (75%) and capsule formulations (47%)
- Plasma exposures increase approximately dose proportional in rats and dogs (toxicological species)
- Accumulation in plasma was minimal after repeat doses
- Doses of 1.5 mg/kg QD were tolerated in mouse and associated with efficacy

# Metastatic uveal melanoma represents a high unmet medical need

**Uveal melanoma (UM)**

- Rare eye cancer: ~5 incidences per million per year in the US
  - Most common intraocular malignancy
- Despite good local disease control (surgery, radiation), ~50% of patients ultimately develop metastasis
- Median survival of 12 months upon detection of metastasis
- Limited treatment options
  - Tebentafusp recently approved in HLA-A2-0201 pts
  - Clinical trial is preferred option for other patients



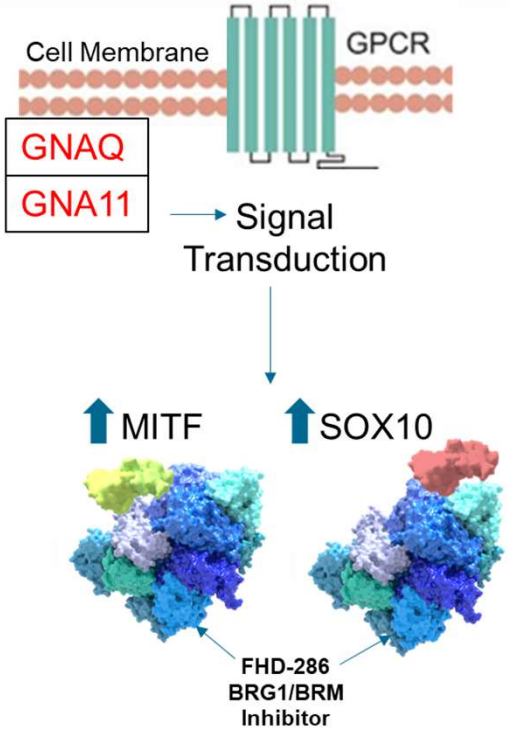



# Therapeutic rationale for uveal melanoma: dependency on overexpression of the MITF / SOX10 transcription factors and the BAF complex

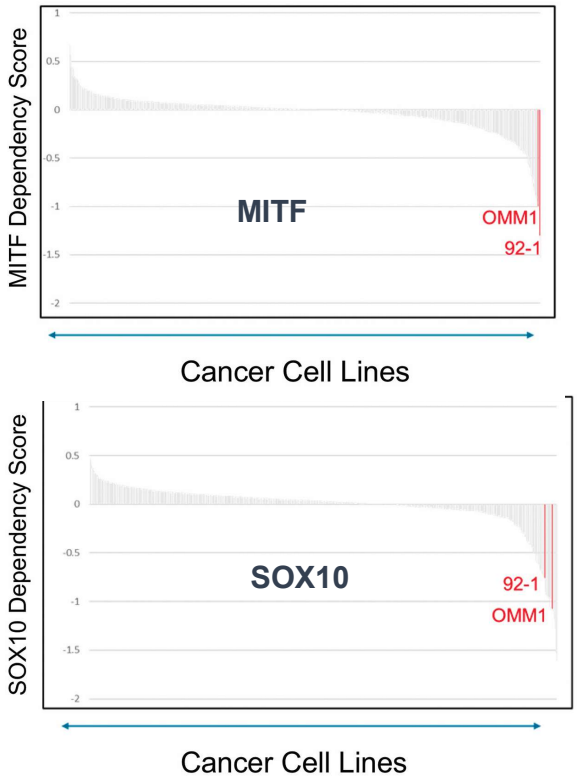
Inhibiting BRM/BRG1 to Shut Down the Abnormal TF Interaction with the BAF Complex

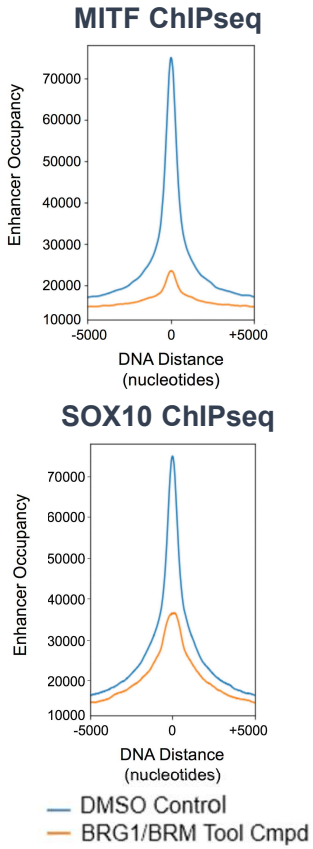
## Biology

**Over 85% of uveal melanoma cancers have GNAQ or GNA11 mutations**




## Validation of Dependency and Approach



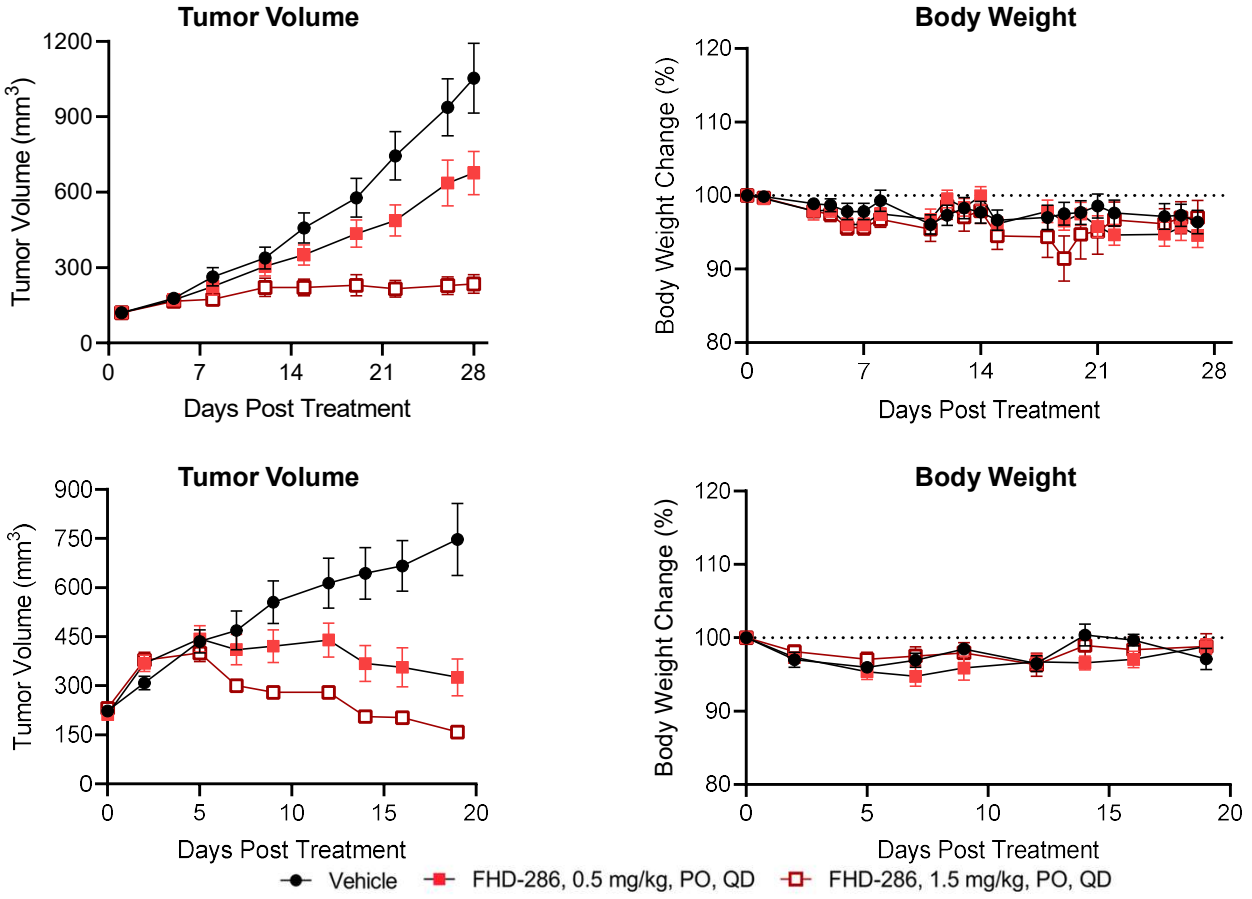
# FHD-286 was associated with dose-dependent tumor regression in uveal melanoma models at tolerated doses

## MP-46 uveal melanoma CDX model

- Dose-dependent tumor growth inhibition
- Well tolerated
- PDX models also showed robust activity

## 92-1 uveal melanoma CDX model

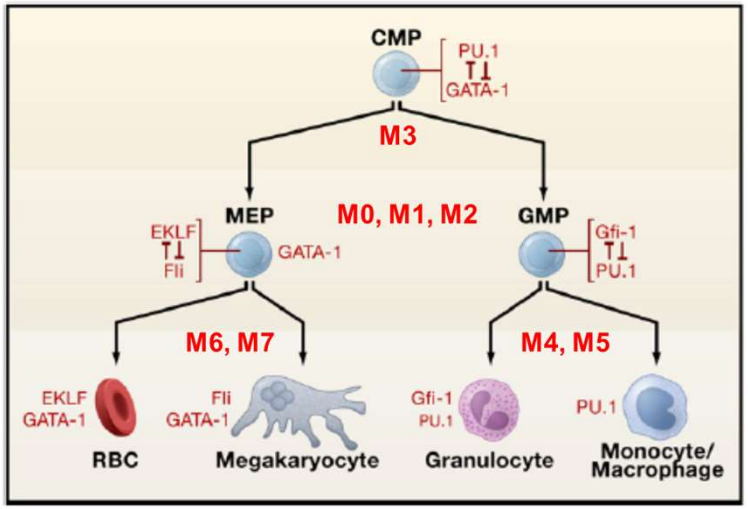
- Dose-dependent tumor growth inhibition
- Tumor regression at 1.5 mg / kg, PO, QD
- Well tolerated



# BAF inhibition has potential utility in AML

- For additional indications, we aim to exploit the centrality of the BAF complex in transcriptional regulation
- Literature has shown that distinct TFs regulate each stage of hematopoietic development
- We believe that there is potential for BAF inhibition to disrupt oncogenic TF activity in an AML sub-type agnostic fashion

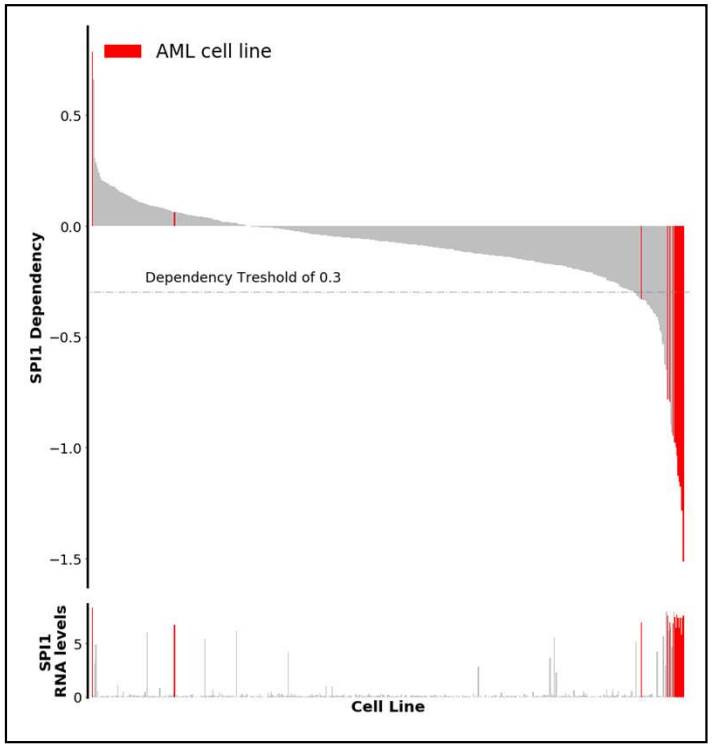
**TF Association with AML**



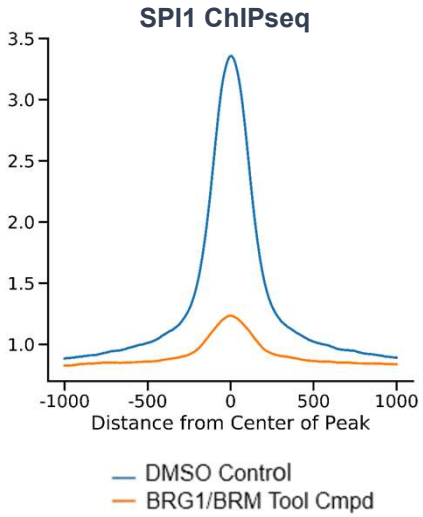

Adapted from: Orkin and Zon, 2008, **Cell**

# AML dependent on BRG1 / lineage TF interaction

## SPI1 (PU.1) / BAF Dependency in M4/M5 derived cell lines




## BRM/BRG1 Inhibition Leads to Loss of SPI1 (PU.1) Occupancy on Chromatin

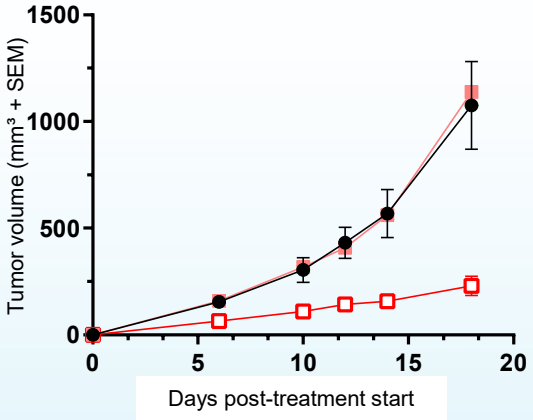


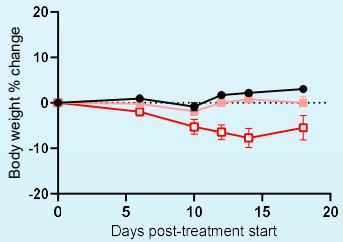

- SPI1 (PU.1) is an example of a TF that plays a central role in M4/M5 AML
- Inhibiting BAF enzymatic activity shuts down SP1 oncogenic activity in M4/M5 subtypes
- We believe that similar BAF/TF interactions drive other AML subtypes, allowing for broad efficacy across AML

See Abstract LB190 – Gabe Sandoval, April 13, 9:00

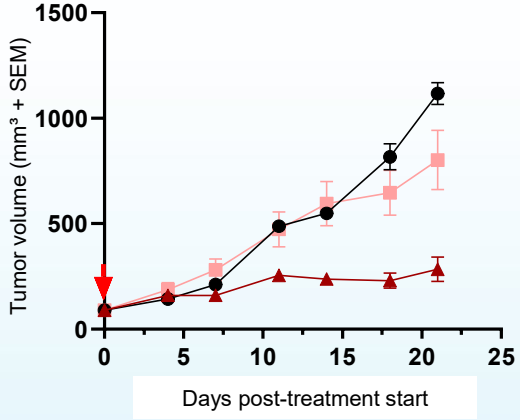
# FHD-286 exhibits significant anti-tumor activity in multiple AML xenograft models

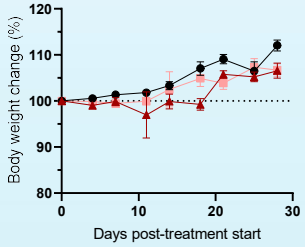
## EOL-1
CDX Model
MLL-PTD (partial tandem duplication)



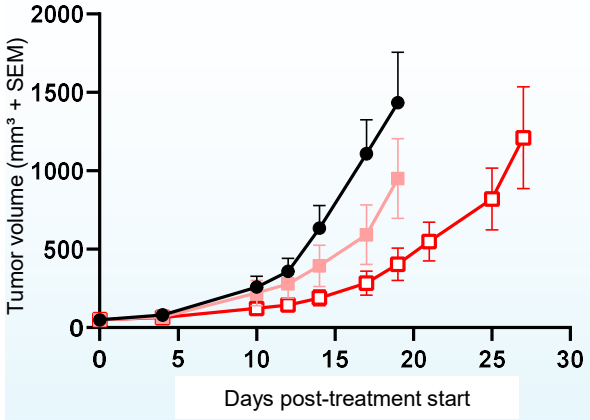



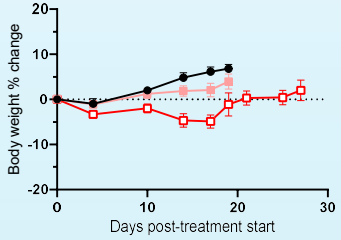

## MV4;11
CDX Model
(FLT3 ITD, MLL-AF4)




## OCI-AML2
CDX Model
(MLL-AF6, DNMT3a mut.)



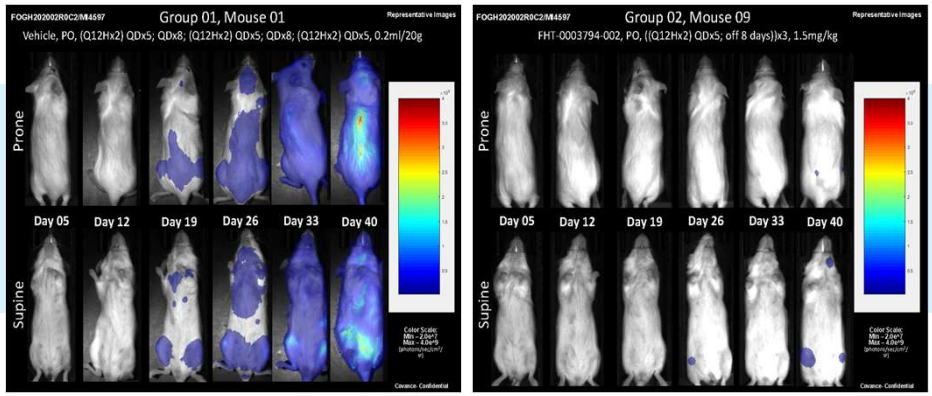




**Vehicle** **FHD-286, 0.5 mg/kg,** QD, p.o **FHD-286, 1.5 mg/kg,** QD, p.o **FHD-286, 1.5 mg/kg,** BID, p.o

# Tumor growth inhibition with FHD-286 treatment observed by bioluminescence

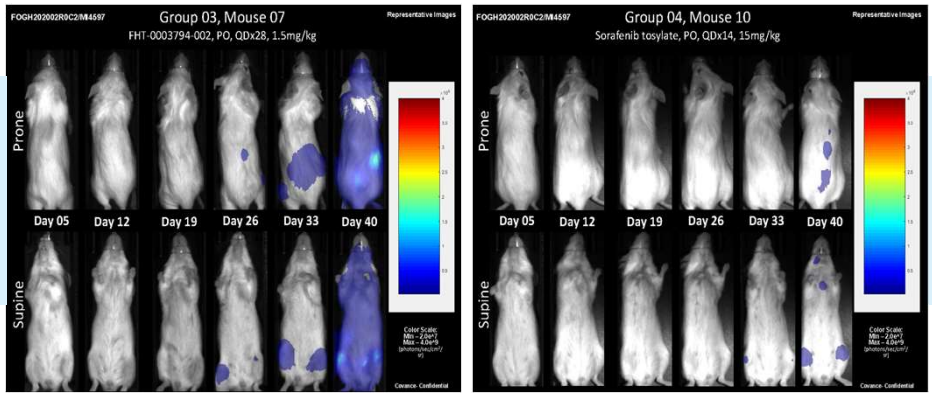
Imaging in a Disseminated AML model

**Vehicle**



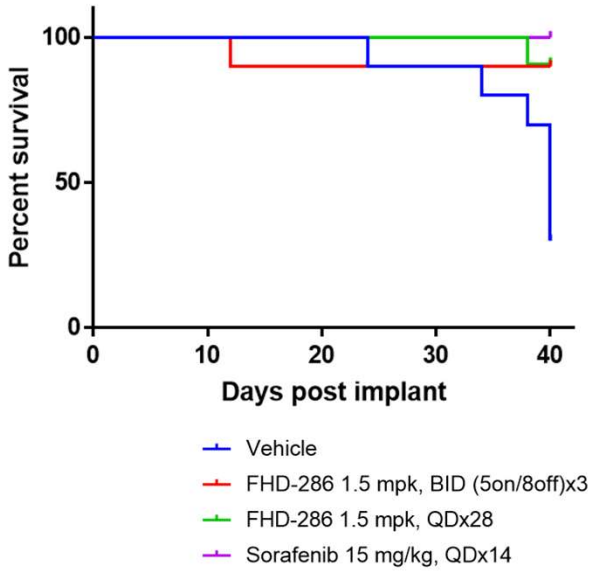

**FHD-286 1.5 mg / kg, BID (5on / 8off) x3**

**FHD-286 1.5 mg / kg QDx28**

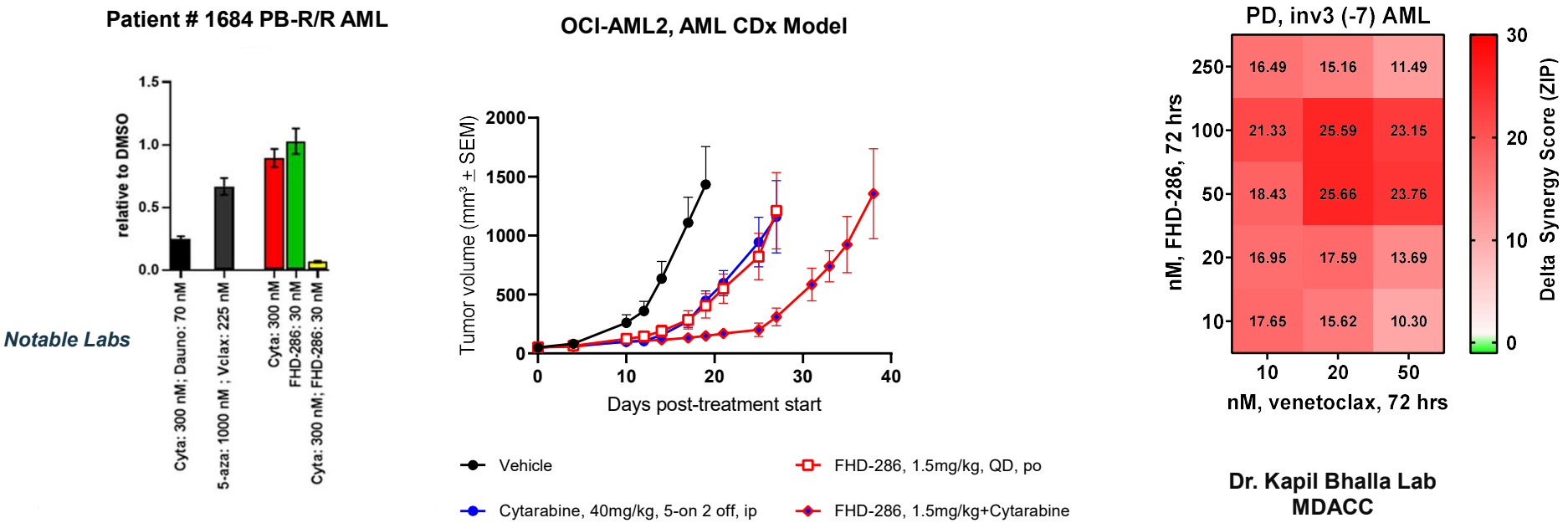



**Sorafenib 15 mg / kg, QDx14**

## FHD-286 Survival Advantage in Disseminated AML Model



# FHD-286 demonstrates the potential for combination in AML lines




- In vitro combination studies in primary patient samples demonstrate potential synergy with multiple partners
- Recent data suggest that inversion 3 / monosomy 7 patients may also benefit from FHD-286 in combination with Venetoclax

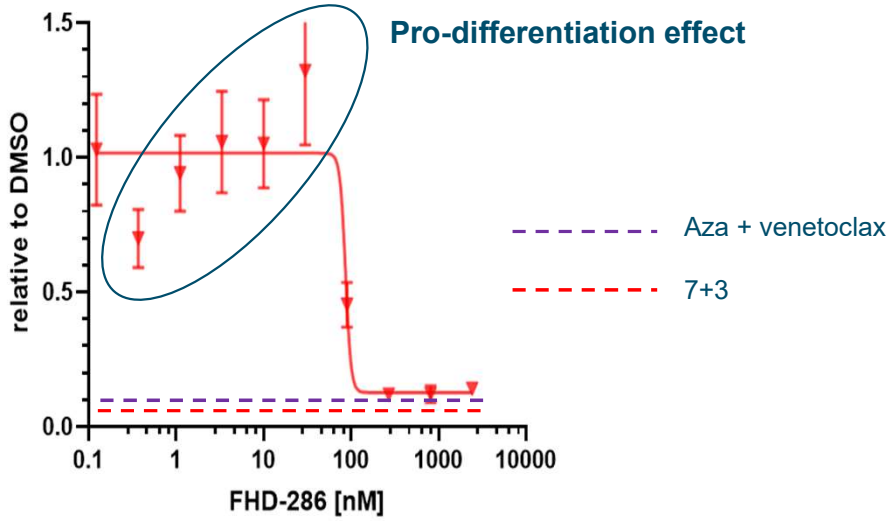
# Preclinical FHD-286 data shows broad efficacy across AML patient-derived samples

| Notable Patient ID | Deep Response | Pathology Review | Disease Status |
|---|---|---|---|
| 1690AML1 | Y | AML | Secondary |
| 1695AML1 | Y | AML/MDS | Secondary |
| 1696AML1 | Y | AML | Secondary |
| 1701AML1 | Y | AML | Secondary |
| 1893AML1 | Y | AML | R/R |
| 1899AML1 | Y | AML | R/R |
| 1990pAML1 | Y | AML | R/R |
| 1991pAML1 | Y | AML | de novo |
| 2041AML1 | Y | N/A | de novo |
| 2043pAML1 | Y | AML | R/R |
| 2059AML1 | Y | AML | R/R |
| 1682AML1 | ~ | N/A | N/A |
| 1689AML1 | ~ | AML/MDS | de novo |
| 1684AML1 | N | AML | R/R |
| 1924AML1 | N | AML/MDS | R/R |

**Notable Labs**

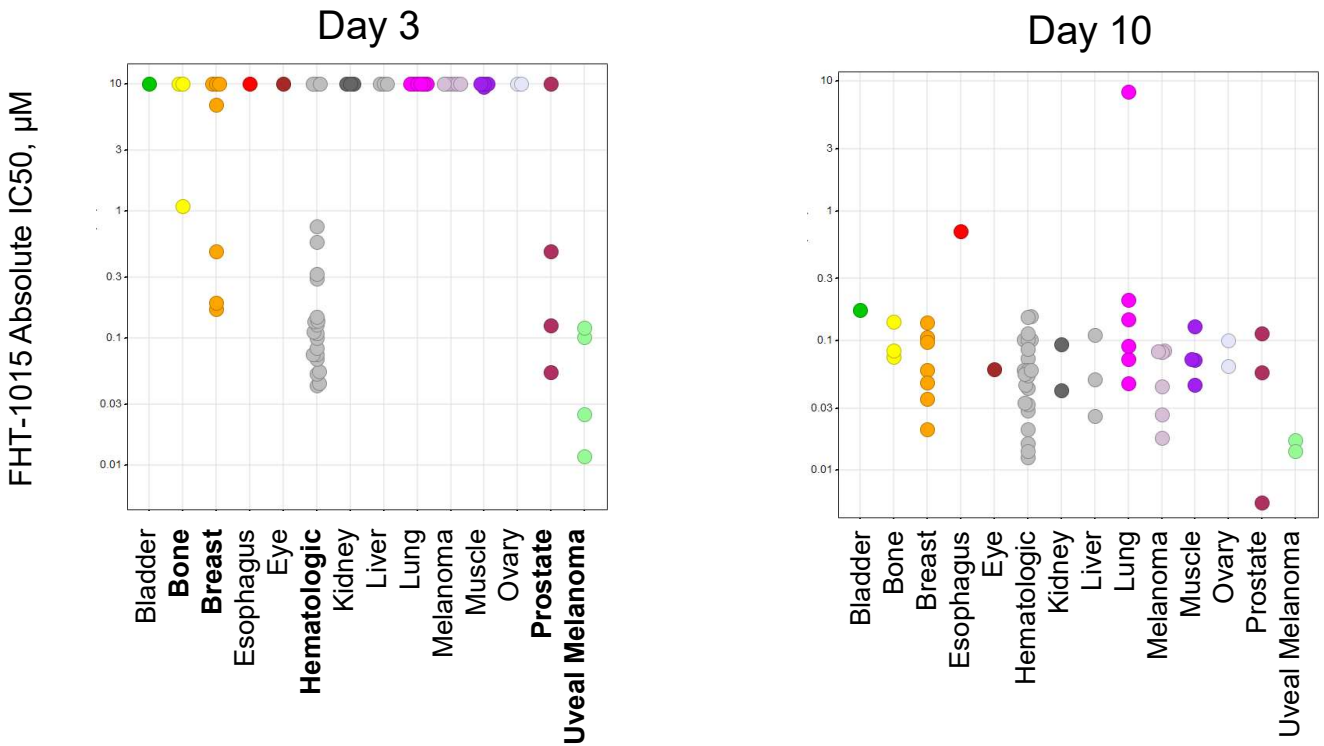
Y = Deep reduction in blast cells
~ = Partial reduction
N = No response

**1695AML1 – BM-secondary AML**




- **Response observed in a majority of primary AML samples, irrespective of prior treatment or disease stage**
- **Orthogonal data set from patient derived samples demonstrate mutation agnostic responses**
- **Currently collaborating with Stephane De Botton at IGR to study the differentiation impact of FHD-286**

# The potential of FHD-286 extends beyond uveal melanoma and AML




- While Uveal Melanoma and AML are sensitive by day 3, other tumor types respond with longer incubation

# FHD-286 clinical development plan

Two Parallel Phase 1 Studies Activated

## CLINICAL PLAN

***AML & Uveal Melanoma FIH Phase 1 Studies***

**Relapsed / Refractory AML & MDS**

**Metastatic Uveal Melanoma**

**Trial Designs**

- Single patient accelerated titration (n=1)
- Convert to 3+3 once relevant PK / PD, safety or clinical activity observed
- Retrospective biomarker analysis to further evaluate safety and efficacy
- Assess safety, PK, biomarkers and efficacy

**Expansion cohorts in AML, UM and potentially other indications**

***Potential for entry into definitive efficacy trials in AML***

***Potential for entry into definitive efficacy trials in metastatic uveal melanoma***

***Potential for indication expansion beyond AML and UM***

# Conclusions

- FHD-286 is a first in class, selective, oral allosteric inhibitor of BRM/BRG1 that has been wholly discovered and developed by Foghorn Therapeutics
- This highly potent compound has demonstrated robust efficacy in multiple xenograft and PDX studies in both uveal melanoma and AML at well tolerated doses
- Following successful completion of 4-week GLP safety studies, Ph1 studies in AML and metastatic uveal melanoma initiated in Q2, 2021, and are currently ongoing
- Additional solid and liquid tumors show sensitivity to BRM/BRG1 inhibition and offer further indication expansion opportunities

# Acknowledgements


## Foghorn thanks all the patients and their families in our ongoing clinical trials

Dr Kapil Bhalla and lab
MD Anderson Cancer Center

Dr Stephane De Botton and lab
Institut Gustave Roussy