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Initial findings from an Ongoing First-in-Human Phase 1 Study of the CBP/p300 Inhibitor FT-7051 in Men with Metastatic Castration-Resistant Prostate Cancer

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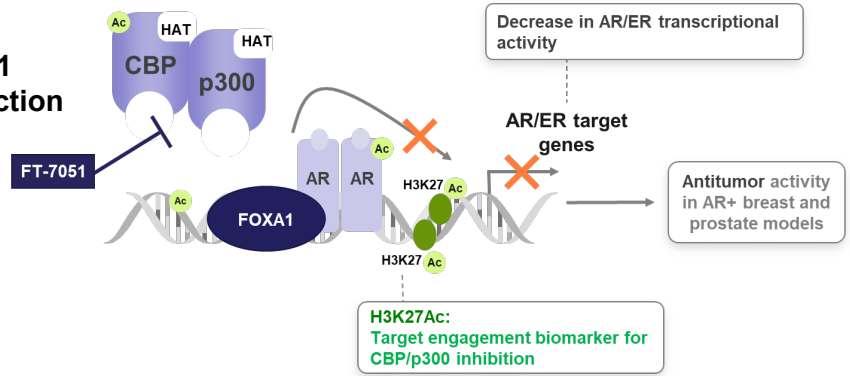
I will discuss the investigational use of FT-7051, an investigational drug, in a First-in-Human study; FT-7051 is an investigational drug – no efficacy or safety claims are intended or implied.

Background

- CBP/p300 are co-activators of the androgen receptor (AR) relevant in metastatic castration-resistant prostate cancer (mCRPC)
  - CBP/p300 is overexpressed in advanced prostate cancer and is upregulated following androgen withdrawal[1]
  - CBP/p300-mediated acetylation of AR, for example, stabilizes the protein and increases AR signaling[2,3]
  - p300 and CBP are involved in androgen-independent transactivation of the AR[4]
- Inhibitors of CBP/p300 targeting the BRD[5,6] and the HAT[7] have shown activity in preclinical models of prostate cancer
- FT-7051, an investigational drug, is an oral, potent, and selective inhibitor of CBP/p300 bromodomain with activity in preclinical prostate cancer models, including those resistant to enzalutamide[8,9]

Figure 1: FT-7051 Mechanism of Action



Ac, acetylation; AR, androgen receptor; BRD, bromodomain; CBP, cyclic adenosine monophosphate-response element binding (CREB) protein binding protein; H3K27, histone H3 at lysine 27; HAT, histone acetyltransferase; p300, E1A binding protein p300

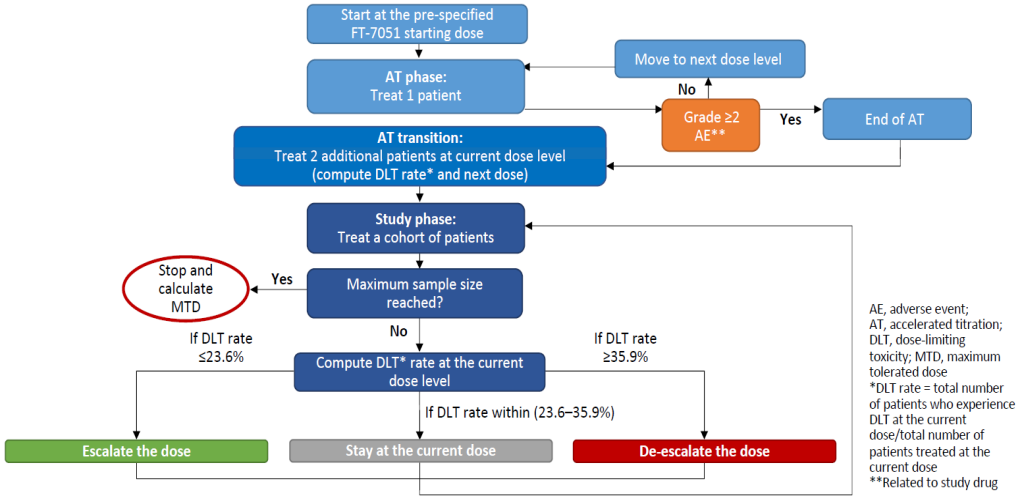
See AACR-NCI-EORTC 2021 Poster P204

Potential Clinical Outcomes:
A CBP/p300 inhibitor may reduce AR transcriptional activity in AR+ cancers and inhibit proliferation

The Courage Study
(7051-ONC-101)

- First-in-human, multicenter, phase 1, open-label study (NCT04575766)
- Bayesian optimal interval (BOIN) design with an accelerated titration (AT) phase
  - Compared with the standard '3+3' design, the advantages of the BOIN design include a higher probability of selecting the correct maximum tolerated dose (MTD) and a lower risk of exposing patients to sub-therapeutic or overly toxic doses[10]
- FT-7051 is administered orally on a 28-d cycle (21-d on / 7-d off)

Figure 2: BOIN Design



The primary study objectives are to evaluate the safety and tolerability of FT-7051 and determine the recommended phase 2 dose of FT-7051 through assessments of:

- Dose limiting toxicities (DLTs)
- Clinically relevant adverse events (AEs) and SAEs
- Clinically relevant safety laboratory values

Key secondary endpoints include:

- % change in PSA from baseline to 12 weeks and maximum decrease in PSA from baseline
- Time to PSA progression
- Time to radiographic progression (soft tissue per RECIST 1.1; bone lesions per PCWG3)
- Overall response rate and radiographic response rate (per RECIST 1.1) for soft tissue lesions
- Complete response rate for patients with bone lesions (per PCWG3)

Patient Population

Key Inclusion Criteria:

- Diagnosis of mCRPC with either adenocarcinoma or mixed histology
  - At least 1 prior line of treatment for mCRPC (prior taxane therapy is allowed)
  - Evaluable disease at enrollment, **and**
  - Rising PSA levels
- Previous failure with at least 1 approved AR pathway inhibitor (eg, abiraterone, enzalutamide, apalutamide, or darolutamide)

Key Exclusion Criteria:

- Prior anticancer treatment with:
  - Small molecules within 4 weeks
  - Prior radiation therapy within 4 weeks
  - Prior androgen antagonist therapy within 2 weeks
  - Prior radium-223 therapy within 6 weeks

Enrollment:

- Eight patients enrolled as of 01-Sep-2021
  - 3 (38%) ongoing
  - 5 (63%) discontinued

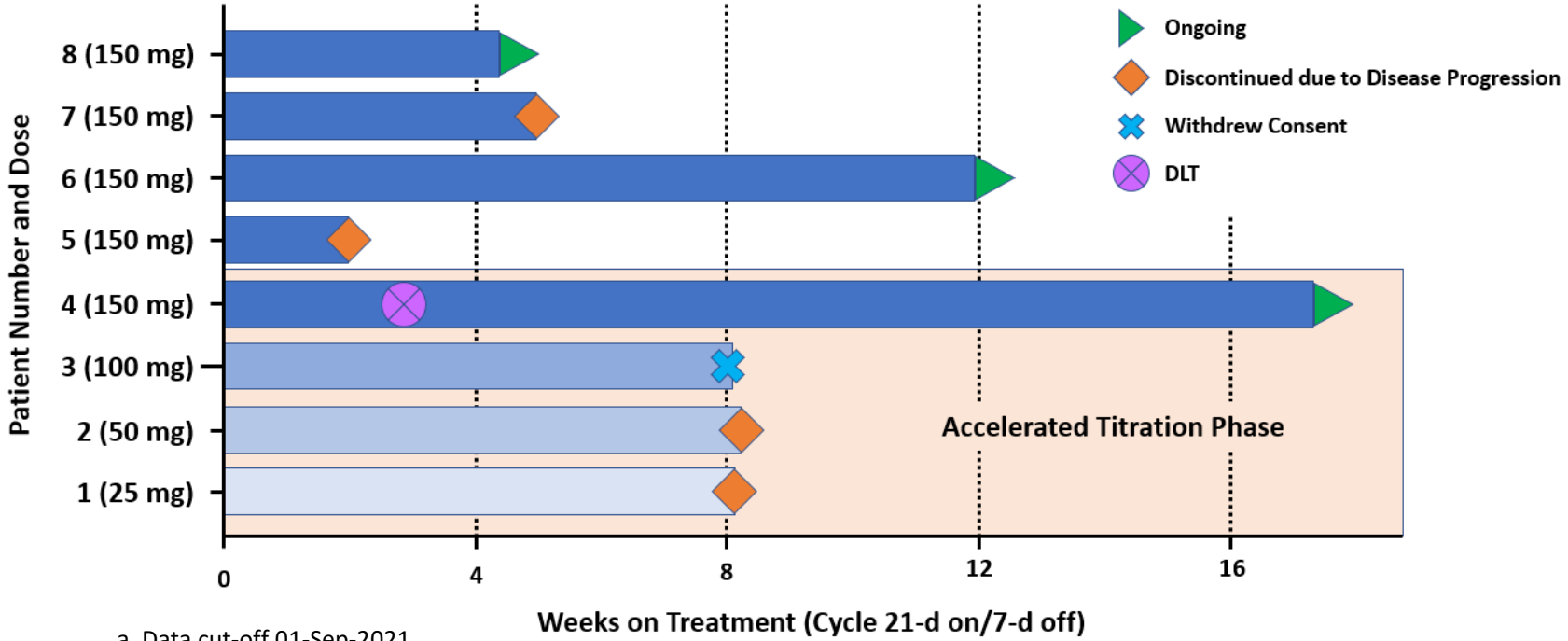
Table 1: Summary of Baseline Characteristics

Parameter	Median (range) or n (%)
Age, years	70 (64-82)
Race:	
White	8 (100%)
Ethnicity:	
Hispanic or Latino	1 (13%)
Not Hispanic or Latino	7 (88%)
Years since first mCRPC diagnosis	2.0 (0.4-5.3)
Prior lines of mCRPC therapy	3.0 (1-6)
Prior taxane therapy for mCRPC	7 (88%)
Baseline PSA, ng/mL	89.4 (12.2 - 1799)
Visceral disease progression	4 (50%)
Nodal disease progression	5 (63%)
Bone disease progression	7 (88%)
AR-v7+ at baseline	4 (80%) [a]

a. AR-v7+ via Rarecyte assay; n=5 evaluable

Time on Treatment and Disposition

Figure 3: Summary of Time on Treatment and Patient Disposition [a]



a. Data cut-off 01-Sep-2021

Safety

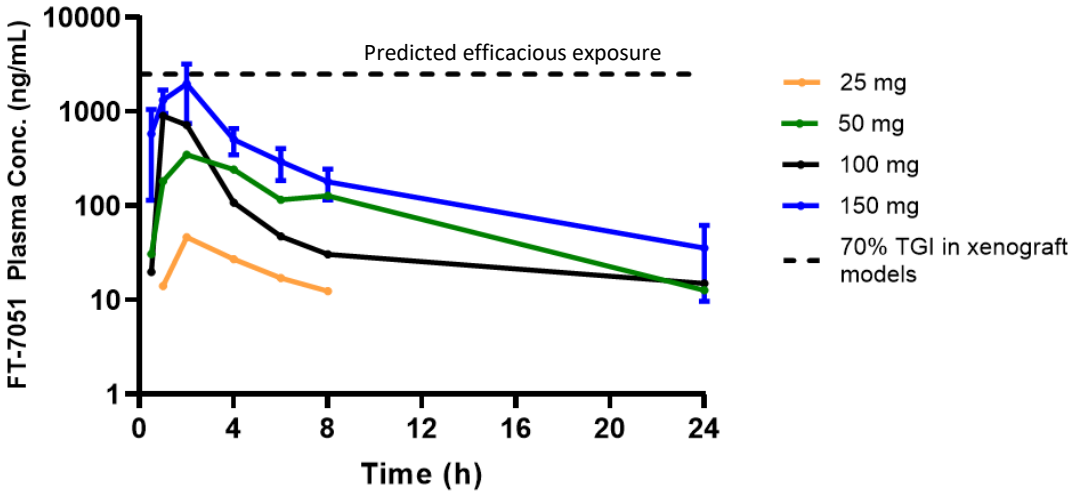
Table 2: Treatment-Emergent AEs (TEAEs) Reported in ≥2 Patients

Preferred Term	Grade 1-2 (N = 8)	Grade 3-5 (N = 8)	Overall (N = 8)
Diarrhea	4 (50%)	0	4 (50%)
Nausea	4 (50%)	0	4 (50%)
Fatigue	3 (38%)	0	3 (38%)
Blood creatinine increased	2 (25%)	0	2 (25%)
Decreased appetite	2 (25%)	0	2 (25%)
Dizziness	2 (25%)	0	2 (25%)
Vomiting	2 (25%)	0	2 (25%)
Weight decreased	2 (25%)	0	2 (25%)

- Most TEAEs were mild (Gr1) or moderate (Gr2) with no events leading to treatment discontinuation
  - One DLT (Gr3 hyperglycemia, possibly related)
    - Medical History: BMI 30.8, Gr2 hyperlipidemia
    - Dose reduced from 150 mg to 100 mg; patient ongoing at 100 mg
    - Managed with insulin and metformin
  - Three patients had disease progression of prostate cancer (Gr3 in one patient; Gr5 in two patients)

Pharmacokinetics

Figure 4: FT-7051 Plasma Concentration – Time Curve



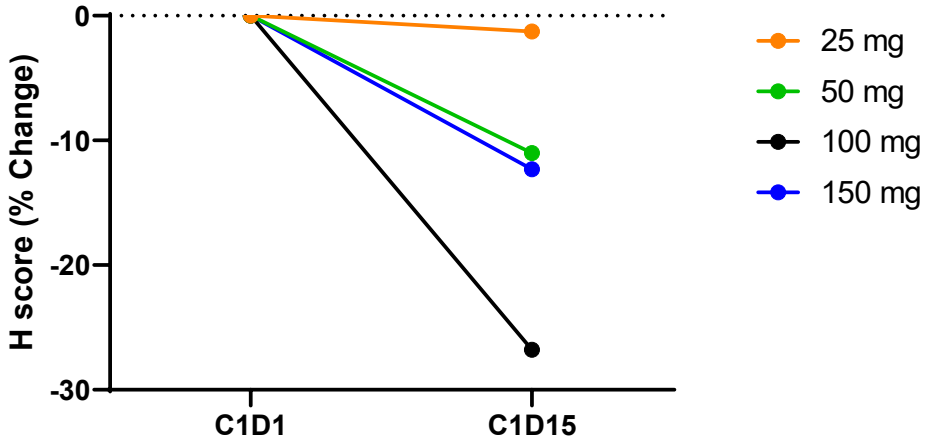
Values reported as mean ± SD for 150 mg (N=4).
TGI, tumor growth inhibition

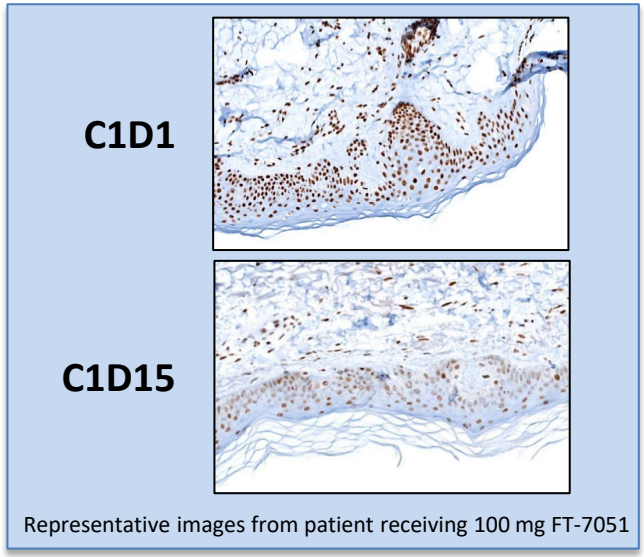
- FT-7051 is rapidly absorbed following oral administration (T_{max}: 1 - 2 hr) with an estimated elimination half-life ($t_{1/2}$) of ~ 5 hr
- Systemic exposure at 150 mg is approaching the predicted efficacious exposure target derived with PK/efficacy modeling[11]

Target Engagement Analysis

- Reductions in nuclear H3K27Ac staining intensity in skin biopsy samples provide preliminary evidence of target modulation

Figure 5: Change from Baseline in H3K27Ac Staining Intensity





Representative images from patient receiving 100 mg FT-7051

Patient Vignette

One patient in the 150 mg cohort experienced Gr3 hyperglycemia (DLT) and achieved a confirmed >50% decrease in PSA with continued decline and ongoing stable disease as of the data cutoff

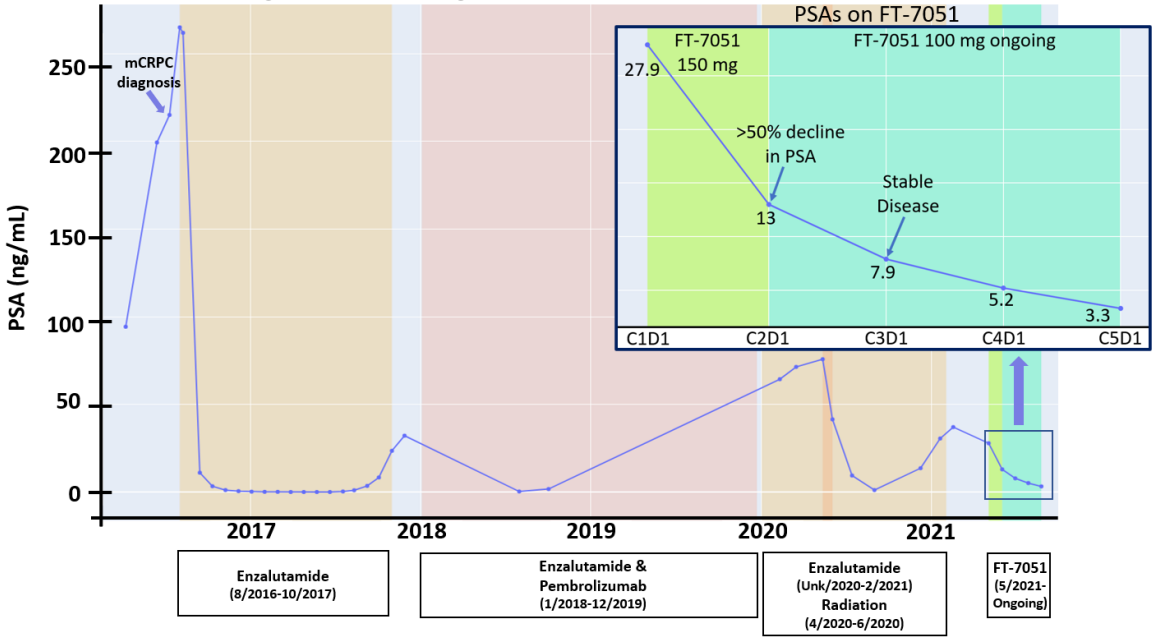
Baseline Characteristics

- Demographics: 66-year-old white male
- Node-only measurable disease
- Chemotherapy naïve with prior enzalutamide, pembrolizumab, and radiation

Biomarker Data

- Positive for AR F877L mutation
- No CTCs at baseline for AR-v7 testing

Figure 6: Single Patient PSA Over Time



Summary

- Available safety data suggest that FT-7051 is well tolerated
  - One DLT (hyperglycemia) reported for a patient receiving 150 mg FT-7051; patient was dose reduced (100 mg) and remains on study as of the data cutoff with a >50% reduction in PSA levels
- Preliminary PK data indicate that FT-7051 exposure is approaching the predicted efficacious exposure threshold determined by PK/efficacy modeling
- Preliminary analysis of target engagement biomarker in surrogate tissue suggests pathway modulation at the exposures tested

These early data support the continued investigation and dose finding of FT-7051 in this ongoing study

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- This study is funded by Forma Therapeutics, Inc., Watertown, MA
- FT-7051 is an investigational drug; no efficacy or safety claims are intended or implied

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