PRE-Clinical Data: In Vitro

**CFT1946 Background**

- **CFT1946 is a novel, orally bioavailable, bifunctional degradation activating compound, or BiDAC™ degrader.**
- **CFT1946 selectively inhibits and degrades mutant BRAF V600 protein.**
- **District from approved BRAF inhibitors, CFT1946 avoids paradoxical RAF activation as the degraded BRAF V600 protein can no longer incorporate into a dimeric signaling complex.**
- **CFT1946 is selective for the mutant proteins and spares wild type V600 BRAF.**
- **Mechanism of action (Figure 2).**
- **CFT1946 induces tumor cell death in BRAF mutant melanoma xenografts and in vivo model, including models resistant to BRAF inhibitors (Figures 3-5).**

**Pre-clinical data provide rationale for a first-in-human (FIH) study to evaluate CFT1946 in BRAF V600 mutant solid tumors.**

**Figure 3: CFT1946 is an On-Mechanism, CRBN-Based, Highly Selective BRAF V600 BiDAC™ Degrader**

- **A. CFT1946 Degrades BRAF V600 in a Dose-Dependent Manner.**
- **B. CFT1946 is an On-Mechanism BiDAC™ Degrader.**
- **C. Proteome Profiling Demonstrates Selectivity of CFT1946 for BRAF V600.**

**Figure 4: Dose Proportional PK and PD Profile in the BRAF V600 A375 Xenograft Mouse Model for CFT1946 Compound**

- **A. Dose Proportional PK and PD for CFT1946.**
- **B. Vehicle, PO BID**
- **C. Enzalutinib, 35 mg/kg PO OD**
- **CFT1946, 0.3 mg/kg PO BID**
- **CFT1946, 3 mg/kg PO BID**
- **CFT1946, 10 mg/kg PO BID**

**Figure 5: CFT1946 Induces Tumor Regression in the A375 (homozygous BRAF V600E) Xenograft Mouse Model as a Single Agent and in Combination With the MEK Inhibitor, Trametinib, in a BRAF Inhibitor-Resistant Xenograft Mouse Model**

- **Vehicle, PO BID**
- **Encorafenib, 35 mg/kg PO OD**
- **CFT1946, 0.3 mg/kg PO BID**
- **CFT1946, 3 mg/kg PO BID**
- **CFT1946, 10 mg/kg PO BID**

**Figure 6: CFT1946 Study Design**

- **Phase 1/2: First-in-Human Clinical Study Design**

**References**

- **CFT1946 Study Design**

**Dose Escalation Monotherapy:

- **A.** CFT1946 administered in 28-day cycle with disease progression or unacceptable toxicity.
- **B.** Dose escalation phase 1 starts at 0.3 mg/kg PO BID (CFT1946 monotherapy).
- **C.** Dose escalation continues in 2-fold increments on a 28-day cycle until first dose-limiting toxicity (DLT). Tumor burden is assessed at baseline and at day 29.**