The Discovery and Characterization of CFT1946: A Potent, Selective, and Orally Bioavailable Degrader of Mutant BRAF for the Treatment of BRAF-driven Cancers

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C4 Therapeutics, Inc.
Watertown, MA

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Christopher G. Nasveschuk

• I have the following financial relationships to disclose:
  • Stockholder in: C4 Therapeutics, Inc.
  • Employee of: C4 Therapeutics, Inc.
Forward-looking Statements and Intellectual Property

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Mechanism of Action for BRAF-V600X Driven Human Cancers

NORMAL CONDITION

BRAF is a serine/threonine protein kinase in the MAPK pathway that promotes cell proliferation and survival when activated through extracellular signals.

BRAF-V600X CONDITION

- Constitutively active BRAF-V600X causes uncontrolled MAPK signaling, leading to tumorigenesis and tumor growth.
- Decreasing BRAF-V600X activity in these cancers leads to growth arrest, cell death, and tumor regression.
- BRAF-V600X is a clinically validated oncology target, however limitations in currently approved inhibitors highlight the need for additional BRAF-V600X targeted therapies.

MAPK, MAP kinase.
Utilizing a Degrader Approach to Overcome Limitations of BRAF Inhibition

**Degrader Rationale**

1. **Application of Inhibitor Drug**
   - BRAF V600E, wtRAF
   - Inhibitor causes paradoxical activation of wildtype RAF

2. **Application of Degrader Drug**
   - CFT1946
   - Degrader prevents dimer formation and avoids paradoxical activation

**Advantages of BRAF V600X Degradation**

- Specifically target mutant BRAF-V600X over wildtype BRAF
- Prevent mutant BRAF-V600X incorporation into RAF dimers
- Avoid paradoxical activation of RAF dimers
- Address failures in inhibitor-based therapy due to resistance mechanisms
- Effect deep elimination of mutant BRAF signaling and create durable responses

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Targeted Protein Degradation Leverages the Body’s Natural Process to Destroy Disease-Causing Proteins

1. Disease-causing Target Proteins
2. Target-Ligase Complex Assembly
3. Ubiquitination of Target
4. Release of Target for Degradation
5. Target Protein Destroyed by Proteasome
6. This recursive process can occur thousands of times with a single degrader molecule before it is eventually cleared by the body.
7. A single degrader drug can eliminate multiple disease-causing proteins through proteasome degradation of the target protein.

BiDAC: Bifunctional Degradation Activating Compound

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Known BRAF V600E Selective Degraders

**Features of known BRAF\textsuperscript{V600E} Degraders**

- Selectively degrade BRAF\textsuperscript{V600E}, while sparing BRAF\textsuperscript{WT}
  - Potentially paradoxical inducer
  - Limited in vivo PK and efficacy data known
    - SJF-0628 showed in vivo efficacy in SK-MEL-246 xenograft mouse model via IP administration

**Strategies to develop BRAF\textsuperscript{V600E} Degraders for oral dosing**

- Focus on paradox breaking BRAF ligands
- Aim to deliver orally bioavailable BiDAC\textsuperscript{TM} degrader using CRBN binder

BiDAC: Bifunctional Degradation Activating Compound
Scaffold Hopping to Address Pharmacokinetics (PK) and Solubility Challenge

**Binds BRAF**

**Binds CRBN**

**Compound 3**
Azaindole core

Mouse IV Cl = 10.8 mL/min/kg
PO DN_AUC = 152 (ng*h/mL)/(mg/kg)
F = 10%

**Compound 4**
Quinazolinone core

Mouse IV Cl = 1.8 mL/min/kg
PO DN_AUC = 1345 (ng*h/mL)/(mg/kg)
F = 14%

Advantages of BRAF quinazolinone BiDAC™ degraders:
- Lower mouse IV PK clearance
- Higher mouse oral exposure and bioavailability
- Generally more soluble

**Strategy:** Identify a quinazolinone-based BRAF degrader suitable for oral dosing

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Rigidifying Spacer Region Improved Degradation Efficiency and PK

BRAF BiDAC degrader with spirocyclic spacer:
- Sample narrower, focused ternary complex regions that favor more catalytically efficient poses
- Lowered mouse IV PK clearance
- Improved mouse oral bioavailability

<table>
<thead>
<tr>
<th></th>
<th>Compound 5</th>
<th>Compound 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotatable Bonds</td>
<td>15</td>
<td>▼ 12</td>
</tr>
<tr>
<td>BRAF-V600E DC$<em>{50}$ / $E</em>{\max}$ [6 h]</td>
<td>71 nM / 28%</td>
<td>53 nM / 19%</td>
</tr>
<tr>
<td>Mouse IV Cl [mL/min/kg]</td>
<td>12.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Mouse F [%]</td>
<td>14</td>
<td>40</td>
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</table>

* CRBN proteins removed for clarity
Binary Binding Potency on Both Ends of a BiDAC Degrader Impacted Degradation Efficiency

<table>
<thead>
<tr>
<th></th>
<th>Compound 7</th>
<th>Compound 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scaffold</strong></td>
<td>Azaindole</td>
<td>Quinazolinone</td>
</tr>
<tr>
<td>BRAF-V600E Ki [nM]</td>
<td>17</td>
<td>▼ 0.1</td>
</tr>
<tr>
<td>CRBN FP Kd [nM]</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td><strong>BRAF-V600E</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC$<em>{50}$ / $E</em>{\max}$ [6 h]</td>
<td>8 nM / 18%</td>
<td>92 nM / 41%</td>
</tr>
</tbody>
</table>

Ki, inhibitory constant; FP, fluorescence polarization; Kd, dissociation constant
Binary Binding Potency on Both Ends of a BiDAC Degrader Impacted Degradation Efficiency

<table>
<thead>
<tr>
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<th>Compound 4</th>
<th>Compound 8</th>
<th>Compound 9</th>
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<tbody>
<tr>
<td><strong>Scaffold</strong></td>
<td>Azaindole</td>
<td>Quinazolinone</td>
<td>Quinazolinone</td>
</tr>
<tr>
<td>BRAF-V600E Ki [nM]</td>
<td>17</td>
<td>▼ 0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>CRBN FP Kd [nM]</td>
<td>92</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td><strong>BRAF-V600E</strong></td>
<td><strong>DC₅₀ / E_max [6 h]</strong></td>
<td><strong>8 nM / 18%</strong></td>
<td><strong>59 nM / 31%</strong></td>
</tr>
<tr>
<td><strong>DC₅₀ / E_max [6 h]</strong></td>
<td>92 nM / 41%</td>
<td></td>
<td><strong>39 nM / 17%</strong></td>
</tr>
</tbody>
</table>

Ki, inhibitory constant; FP, fluorescence polarization; Kd, dissociation constant
Hydrophobic Collapse Improved Oral Bioavailability

Hypothesis:

- In the context of these BRAF BiDAC degraders, piperidine N provided higher propensity for conformation collapse, resulting in lower SASA.
CFT1946 Displays A Balanced Preclinical Profile

<table>
<thead>
<tr>
<th></th>
<th>Compound 3</th>
<th>Compound 5</th>
<th>Compound 6</th>
<th>CFT1946</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF DC\textsubscript{50} / E\textsubscript{max} [24 h]</td>
<td>2 nM / 7%</td>
<td>23 nM / 11%</td>
<td>30 nM / 11%</td>
<td>14 nM / 26%</td>
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<tr>
<td>A375 NRAS\textsuperscript{Q61K} * pERK 1 h [nM]</td>
<td>115</td>
<td>317</td>
<td>120</td>
<td>42</td>
</tr>
<tr>
<td>A375 NRAS\textsuperscript{Q61K} * GI\textsubscript{50} 96 h [nM]</td>
<td>96</td>
<td>&gt;3000</td>
<td>149</td>
<td>150</td>
</tr>
<tr>
<td>HepG2 GI\textsubscript{50} [mM]</td>
<td>3.3</td>
<td>&gt;10</td>
<td>0.3</td>
<td>&gt;10</td>
</tr>
<tr>
<td>CL\textsubscript{obs} Mouse / Rat [mL/min/kg]</td>
<td>10.8 / 0.9</td>
<td>12.8 / 0.9</td>
<td>3.5 / 1.0</td>
<td>0.8 / 0.5</td>
</tr>
<tr>
<td>F % Mouse / Rat</td>
<td>10 / 3</td>
<td>14 / 13</td>
<td>40 / 24</td>
<td>89 / 89</td>
</tr>
</tbody>
</table>

\* An engineered disease-relevant BRAF inhibitor resistant cell line
CFT1946 is an On-Mechanism, CRBN-Based, BRAF-V600X BiDAC™ Degrader

CFT1946 Degrades BRAF-V600E in a Dose Dependent Manner

- HiBiT assay shows BRAF-V600E degradation with CFT1946 treatment in dose-dependent manner
- pERK loss aligns with loss of BRAF-V600E protein demonstrating MAPK pathway inhibition

DC₅₀ = 14 nM
Eₘₐₓ = 26%

CFT1946 (100 nM) in A375 cells @ 24 h

- BRAF-V600E degradation with CFT1946
- No BRAF-V600E degradation with ligand competition, CRBN ligand competition, inhibition of CUL4 E3 with MLN4924 or inhibition of the proteasome with bortezomib

HiBiT; high affinity bioluminescent tag; IMiD, immunomodulatory imide drug.
C4 Therapeutics data on file.
CFT1946 Degrades BRAF-V600E with No Activity on WT-BRAF, CRAF, or ARAF

Proteome Profiling Demonstrates Selectivity of CFT1946 for BRAF-V600E

Proteome Profiling in WT-BRAF Cells Demonstrates Selectivity of CFT1946 for mBRAF

C4 Therapeutics data on file.
CFT1946 Causes BRAF-V600E Degradation, Potent Inhibition of MAPK Signaling, & Loss of Viability in BRAF-V600E Cells but Not in WT-BRAF Cells

*note: CFT1946\textsuperscript{NMe} is a non-CRBN binding version of CFT1946; BRAF is BRAF-V600E

MAPK, MAP kinase.

C4 Therapeutics data on file.
CFT1946 Induces Tumor Regression in the BRAF-V600E A375 Xenograft Mouse Model in Accordance with PK/PD Results

CFT1946 Treatment of A375 Cell Line in vivo Shows Dose-Dependent Tumor Regression Superior to Inhibitor

CFT1946 dose-response xenograft data demonstrates that 10 mg/kg BID dose results in sustained tumor regression and is the minimum efficacious dose.

Dose Proportional PK and PD for CFT1946 Observed After Single Dose PO Treatment

BID, twice a day; MAPK, MAP kinase; PO, by mouth; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily.

C4 Therapeutics data on file.

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Combination Treatment of BRAFi Resistant Xenograft Model with CFT1946 and MEKi Shows Tumor Growth Inhibition/Regression

CFT1946 as a Single Agent and in Combination with MEKi is Effective in MAPK Pathway Inhibition, Superior to BRAFi

BID, twice a day; BRAFi, BRAF inhibitor; MAPK, MAP kinase; MEKi, MEK inhibitor; PO, by mouth; PK/PD, pharmacokinetics/pharmacodynamics; QD, once daily. C4 Therapeutics data on file.

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CFT1946 is a potent and mutant-selective BiDAC™ degrader of BRAF-V600E and superior to inhibitors in in vitro and in vivo models with BRAF-V600E–driven disease and in the escape mutant BRAF-V600E/NRAS-Q61K–driven model.

The medicinal chemistry path leading to CFT1946 demonstrates that it is possible to access catalytically efficient and orally bioavailable degraders through rational ligand and linker modifications.

Based on the preclinical profile, CFT1946 is currently being evaluated in a Phase 1 trial in patients with both BRAF-V600X–driven cancers and inhibitor-resistant BRAF-V600X–driven cancers.
Acknowledgments

Thank you to the C4T scientists & our CRO partners across the globe who made this work possible