CFT7455: A novel, IKZF1/3 Degrader That Demonstrates Potent Tumor Regression in a Spectrum of Non-Hodgkin Lymphoma Xenograft Models

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Abstract #233

Introduction
Ikaria family zinc finger protein 1 and 3 (IKZF1/3) are essential transcription factors (TF) for differentiation of B and T lymphocytes. IMiDs (e.g. pomalidomide [pom]) degrade IKZF1/3 via interaction with the cereblon (CRBN) E3 ligase and have shown promise in NHL. Preclinical data suggest improvements in IKZF1/3 degraders may lead to enhanced efficacy. CFT7455 is a novel IKZF1/3 degrader optimized for high affinity CRBN binding and IKZF1/3 degradation, resulting in downregulation of the interferon regulatory factor 4 (IRF4), a critical regulator in non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and peripheral T-cell lymphoma (PTCL).

Methods:
Protein expression in DLBCL and mantle cell tumor xenografts were quantified by immunohistochemistry or target mass spectrometry. Cell viability were monitored by CellTiter-Glo. Tumor xenograft studies were conducted by implanting human NHL lines into immunocompromised mouse strains.

Results:
CFT7455 potency in cell-based CRBN competition studies (IC50 = 0.4 nM) in the ALK+ anaplastic large cell lymphoma (ALCL) line KJK, CFT7455 treatment led to degradation of IKZF1/3, which was blocked by proteasome or NEDD8 inhibition, demonstrating on-mechanism activity. CFT7455 demonstrated potent antiproliferative activity across a panel of NHL cell lines. In EU8 xenograft, pom treatment was ineffective at a clinically relevant dose (3000 µg/kg). CFT7455 treatment (100 µg/kg, PO) resulted in durable tumor regression associated with deep IKZF1/3 degradation and IRF4 downregulation (75% 25% remaining, respectively). CFT7455 showed dose dependent efficacy in the KJK-ALL xenograft model, DL40, from 3-100 µg/kg with regressions at doses ≥10 µg/kg. Global proteomic studies on DL40 xenografts treated with CFT7455 (100 µg/kg, 4 hours) showed only IKZF1/3 were significantly degraded. MCL is characterized by elevated cyclin D1, subsequent release of E2F3 and pathway activation. In the REIC MCL xenograft model, doses of CFT7455 10 µg/kg promoted tumor regression. Pharmacodynamic studies showed that CFT7455 (30 µg/kg) promoted degradation of IRF4 and downregulation of cyclin D1 and E2F3. In a pome immunoassay DLBCL model (TMD8), administration of CFT7455 (100 µg/kg) led to tumor regression. Together these results show that the optimized CRBN binding of IKZF1/3 degrading activity in MCL and sustained degradation of IKZF1/3 and translates to tumor regressions in NHL models.

CFT7455 is a selective, orally available inhibitor of IKZF1/3, with single agent antitumor activity in DLBCL, MCL, and NHL model cells having those isomeric to pom. These results support clinical investigation of CFT7455 for NHL.

CFT7455 Is Positively Addressed IKZF1/3 (Ikaroas) and IKF3 (Aiolos) Dependent Lymphomas

Figure 1: IKZF1/3 dependent lymphomas and mechanism of action for CFT7455

Figure 2: Differential expression and mechanistic effects of CFT7455

Figure 3: CFT7455 displays high affinity CRBN Binding and Potent, Deep IKZF1 Degradation

Figure 4: CFT7455 Demonstrates Potent Antiproliferative Activity in PTCL, DLBCL and MCL Cell Lines

Figure 5: CFT7455's ability to degrade IKZF1/3 in ALCL tumor models

Figure 6: CFT7455 Triggers Caspase-Mediated DLBCL Cell Death and is Efficient in Pemomimotic Model

Reference: