Identification of a Potent KRAS (ON/OFF) Inhibitor Clinical Candidate Series with Selectivity for Mutant KRAS over HRAS and NRAS

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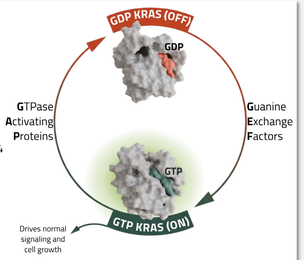
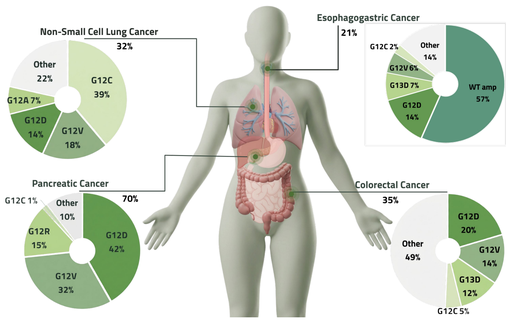
Poster #0410

~15% of All Carcinomas have a KRAS Mutation[1]

- KRAS is a GTPase that cycles between inactive GDP-bound (OFF) and active GTP-bound (ON) states. Oncogenic mutations favor the active GTP-bound (ON) state, driving sustained downstream signaling[2]
- KRAS is most frequently mutated in pancreatic ductal adenocarcinoma, colorectal cancer, and non-small cell lung cancer [1,3,4]
- Activating mutations occur predominantly at codons 12, 13, and 61, with G12D, G12V, and G12C being the most prevalent alleles[1,3,4]





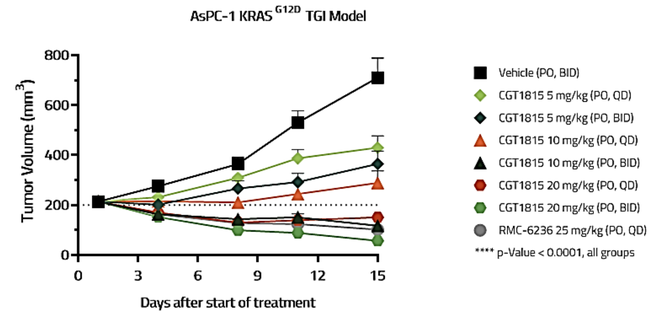
CGT1263 is a Selective Pan-Kras Dual On/Off Inhibitor

- Potently inhibits KRAS across prevalent oncogenic variants
- >500x selectivity for KRAS over HRAS and NRAS isoforms may confer tolerability advantages compared with multi-RAS inhibitors[5]

CGT1263 and Prodrug CGT1815 Key Findings

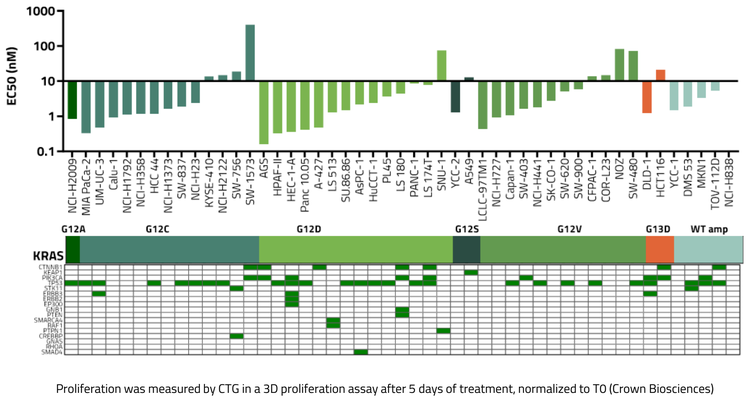
- **Broad Antiproliferative Activity:** CGT1263 inhibited proliferation in a 3D model across a panel of clinically relevant KRAS altered cell lines
- **Orally Delivered Active Moiety Across Species:** Prodrug CGT1815 enabled sustained plasma exposure of active CGT1263 across species
- **Sustained pERK inhibition in a KRAS^{G12D} PK/PD Study:** Oral administration of the prodrug CGT1815 provided CGT1263 exposure with dose-dependent pERK inhibition in an AsPC-1 KRAS^{G12D} model
- **Robust Antitumor Activity:** Oral administration of the prodrug CGT1815 resulted in CGT1263 plasma concentrations with dose-dependent tumor regression in AsPC-1 KRAS^{G12D} xenografts
- **Tumor Selective Pathway Suppression:** Tumor pERK inhibition was achieved with limited skin pathway suppression, supporting a differentiated therapeutic window relative to Mult-RAS (ON) and MEK inhibitors
- **IND-Enabling Studies Ongoing:** IND submission is targeted by year-end 2026

Tumor Regressions in AsPC-1 KRAS^{G12D} TGI Model at 20 mg/kg QD



- Oral administration of CGT1815 at 20 mg/kg QD and 10 or 20 mg/kg BID resulted in tumor regressions equivalent to a 25 mg/kg QD, clinically relevant dose of RMC-6236
- CGT1815 is well tolerated with minimal body weight loss in this mouse model
- Antitumor activity aligned with the CGT1815 PK/PD study affording sustained pERK inhibition

CGT1263 Inhibited Proliferation Across Clinically Relevant KRAS Mutant and Amplified Cancer Cell Line Models

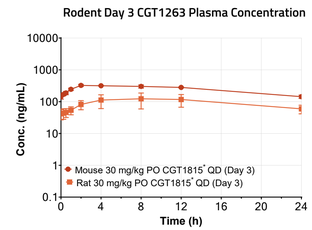


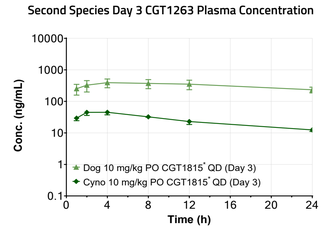
Proliferation was measured by CTG in a 3D proliferation assay after 5 days of treatment, normalized to T0 (Crown Biosciences)

- CGT1263 was evaluated in a clinically relevant 5-day 3D proliferation model across a panel of 56 KRAS-altered cell lines at Crown Biosciences
- In this panel, CGT1263 showed potent inhibition against 14 cancer types, including NSCLC, pancreatic, colorectal, and gastric cancer
- Co-mutations or alterations classified as oncogenic or likely oncogenic in the cell lines are shown in the lower grid[6,7]

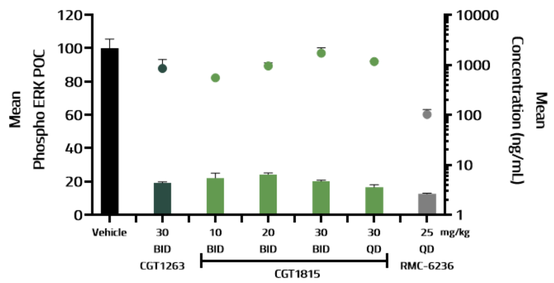
Oral Prodrug CGT1815 Enabled CGT1263 Exposure Across Species

- Oral administration of the prodrug CGT1815 resulted in sustained plasma exposure of active CGT1263 in mouse, rat, dog, and cynomolgus monkey
- Consistent IVIVC across species supports reliable human translational modeling





Steady State PK/PD: pERK Inhibition in a 3-Day AsPC-1 KRAS ^{G12D}



- Oral administration of CGT1263 and the prodrug CGT1815 resulted Robust inhibition of pERK by CGT1263, as measured with HTRF 6-hours post final dose
- Schedule Independence: CGT1815 dosed at 30 mpk QD afforded pERK suppression equivalent to the BID regiment

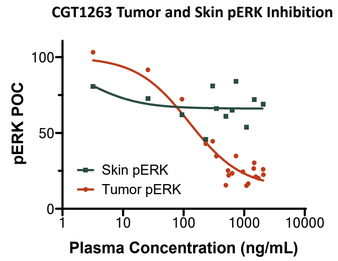
*CGT1815 Dose normalized to CGT1263 molecular weight

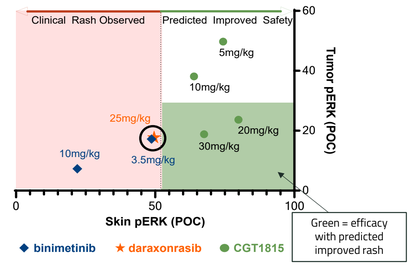
Multi-RAS (ON) and MAPK Inhibitors Induce Rash in the Clinic

- The RAS-MAPK-ERK pathway is essential for skin development and regulating keratinocyte proliferation, differentiation, and survival[8,9]
- Multi-RAS (ON) or MAPK inhibitors induce rash in the clinic due to on-target MAPK pathway inhibition[10,11]

Compound	Clinical Dose	Preclinical Matched Dose	Clinical Rash Incidence (All Grades)
RMC-6236[10]	300 mg*	25 mg/kg	88%
Binimetinib[11]	45 mg*	3.5 mg/kg	77%

Differentiation Between Tumor and Skin pERK Inhibition*





- Novel assay comparing skin vs tumor pERK inhibition shows differentiation between RAS pathway inhibitors: Multi-RAS (ON), MEK and Pan-KRAS CGT1263
- Orally administered CGT1815 gave CGT1263 exposure that did not result in significant inhibition of pERK in the skin while maintaining inhibition of pERK in the tumor
- In contrast, RMC-6236 and binimetinib demonstrated substantial skin pERK inhibition at clinically relevant doses[10,11] that are associated with rash
- Presumably, the lack of HRAS and NRAS inhibition by CGT1262 prevents inhibition of pERK in the skin and could lead to improved clinical skin toxicity outcomes

Single dose binimetinib, daraxonrasib or CGT1815 was orally administered to AsPC-1 tumor bearing mice, with plasma, tumor and skin harvested at peak signal, 2 or 6 hr, post administration

References: 1. AACR Project Genie Consortium. *Cancer Discov.* 2017;16 **2.** Hunter J et al. *Mol Cancer Res*. 2015; 13(9). **3.** Yang Y et al. J. Clin. Med 2023; 12(2). **4.** Moore A et al. Nat. Rev. Drug Discov. 2020; 19(8). **5**. Salituro et al. *EORTC-NCI-AACR Symposium on Mol Targets and Can Thera;* 2025*;* abstr B024 *;* **6**.Suehnholz et al. *Cancer Discov.* 2024. **7.** Chakravarty et al. *JCO PO* 2017. **8.** Drosten et al. *Oncogene.* 2014. **9.** Macdonald J et al. *J AM Acad Dermatol.* 2015; 72(2). **10.** Wolpin et al. *J Clin Oncol.* 2025; 43:abstr TPS4230 **11.** Bendell J et al. *Br J Cancer*. 2017; 116(5).

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