A phase 1/2 trial of FOG-001, a first-in-class direct β-catenin:TCF4 inhibitor
Preliminary safety and efficacy in patients with solid tumors bearing Wnt pathway-activating mutations (WPAM+)

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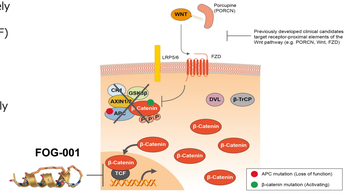
Background

- FOG-001 is a first-in-class and only direct inhibitor of β-catenin that potently, selectively and competitively inhibits the interaction between β-catenin and the T-cell factor (TCF) family of transcription factors, the most downstream node in the Wnt pathway.
- By directly targeting the β-catenin:TCF protein–protein interaction, FOG-001 is downstream of, and thereby targets, virtually all mutations that activate canonical Wnt signaling.
- Preclinical data from mouse efficacy models and toxicology studies demonstrate good tolerability of FOG-001 with a clear therapeutic window.

Figure 1. A Novel β-catenin:TCF4 Inhibitor



Objectives

- In this poster we present safety, efficacy, and pharmacokinetic/pharmacodynamic results from the FOG-001-101 study of FOG-001 in patients with advanced solid tumors.

Methods

Figure 2. FOG-001-101 – A Phase 1/2 Study in MSS CRC and WPAM+ Solid Tumors

Key inclusion criteria:
- ECOG 0-1
- Adequate organ and marrow function
- Part 1a: MSS CRC or WPAM+ solid tumors
- Part 1b: MSS CRC only (PD biomarker cohort)

Key exclusion criteria:
- Bone metastasis, osteoporosis, IBD

Dosing regimen:
- QW IV 4-week cycles

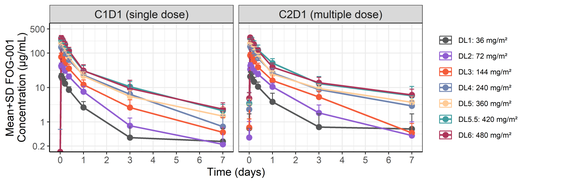
Primary objectives:

Parts 1a:
- Evaluate safety and tolerability of FOG-001 in patients with MSS CRC and WPAM+ solid tumors
- Select preliminary recommended Phase 2 dose (pRP2D)
- Define PK profile and demonstrate pharmacodynamic effects (secondary objective)

Part 1b:
- Identify preliminary biomarkers predictive of efficacy in participants with MSS CRC

Results

Figure 3. FOG-001 Pharmacokinetic Characteristics



FOG-001 has favorable pharmacokinetic characteristics:
- Extensive distribution, dose-proportional exposure, low inter-patient variability.
- Exposures at DL4 and above meet or exceed the efficacious exposures observed in sensitive mouse CRC PDX models.

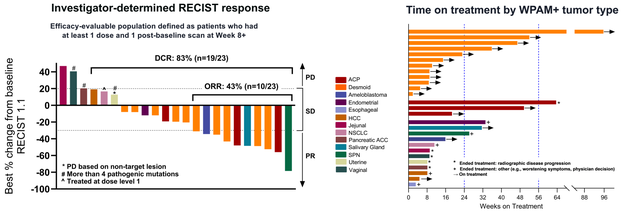
Results

Table 1. Favorable Safety Profile for All Doses Tested: Treatment-related Adverse Events (TRAEs) in Part 1 in ≥10% Patients

	DL1 36 mg/m² (N=3)		DL2 72 mg/m² (N=8)		DL3 144 mg/m² (N=11)		DL4 240 mg/m² (N=18)		DL5 360 mg/m² (N=20)		DL5.5 420 mg/m² (N=13)		DL6 480 mg/m² (N=21)		All participants (N=94)	
	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)
Any TRAE n (%)	0	0	5 (62.5)	0	8 (72.7)	0	17 (94.4)	1 (5.6)	17 (85.0)	3 (15.0)	11 (84.6)	3 (23.1)	21 (100)	14 (66.7)	79 (84.0)	21 (22.3)
Blood bilirubin increased	0	0	0	0	1 (9.1)	0	6 (33.3)	1 (5.6)	5 (25.0)	2 (10.0)	8 (61.5)	1 (7.7)	14 (66.7)	9 (42.9)	34 (36.2)	13 (13.8)
Fatigue	0	0	0	0	2 (18.2)	0	9 (50.0)	0	6 (30.0)	1 (5.0)	3 (23.1)	0	9 (42.9)	1 (4.8)	29 (30.9)	2 (2.1)
Nausea	0	0	1 (12.5)	0	4 (36.4)	0	10 (55.6)	0	3 (15.0)	0	1 (7.7)	0	7 (33.3)	0	26 (27.7)	0
AST increased	0	0	0	0	0	0	6 (33.3)	0	5 (25.0)	0	3 (23.1)	0	11 (52.4)	2 (9.5)	25 (26.6)	2 (2.1)
Hyponatremia	0	0	0	0	1 (9.1)	0	3 (16.7)	0	4 (20.0)	0	5 (38.5)	1 (7.7)	9 (42.9)	3 (14.3)	22 (23.4)	4 (4.3)
Alopecia	0	0	2 (25.0)	0	0	0	6 (33.3)	0	3 (15.0)	0	0	0	5 (23.8)	0	16 (17.0)	0
Decreased appetite	0	0	1 (12.5)	0	2 (18.2)	0	1 (5.6)	0	4 (20.0)	0	0	0	4 (19.0)	0	12 (12.8)	0
Epistaxis	0	0	0	0	0	0	6 (33.3)	0	3 (15.0)	0	1 (7.7)	0	2 (9.5)	0	12 (12.8)	0
Platelet count decreased	0	0	0	0	0	0	2 (11.1)	0	2 (10.0)	0	2 (15.4)	0	5 (23.8)	3 (14.3)	11 (11.7)	3 (3.2)
ALT increased	0	0	0	0	0	0	3 (16.7)	0	1 (5.0)	0	1 (7.7)	0	5 (23.8)	0	10 (10.6)	0

- Most commonly reported TRAEs are low grade with mild symptoms or asymptomatic lab abnormalities that are reversible.
- FOG-001 is a potent inhibitor of the OATP1B1/1B3 transporters which may result in relatively isolated, asymptomatic increases in bilirubin without clinical sequelae.
- No Grade 4 or Grade 5 TRAEs. MTD was not reached. Only 1 DLT was observed at DL6: Grade 3 bilirubin elevation with Grade 2 AST/ALT/Alkaline phosphatase increases. Did not meet Hy's Law criteria.
- Grade 3 TRAEs were manageable; No patients discontinued treatment due to TRAEs.
- Unlike previous Wnt pathway inhibitors (e.g. PORCN, FZD) no high-grade bone toxicity has been observed. No high-grade GI toxicities observed despite pathway being implicated in the GI tract. No high-grade dysgeusia observed.

Figure 4. FOG-001 Efficacy in non-CRC WPAM+ Solid Tumors



- Responses observed across multiple Wnt/β-catenin driven solid tumors, particularly those with low tumor mutational burden including desmoid and adamantinomatous craniopharyngiomas (ACP).
- 10 desmoid patients were response evaluable; of the 5 patients with >1 post-baseline scan, 4 (80%) have had an objective response per RECIST 1.1.

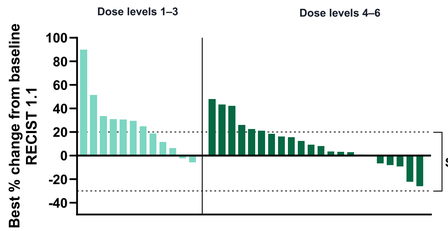
Table 2. Baseline Demographics and Patient Characteristics in CRC

	Patients with CRC (n=67)
Median age (range), years	54.0 (30–77)
Sex, n (%) Male / female	45 (67.2) / 22 (32.8)
Race, n (%) White Black / African American Asian Not reported / missing	54 (80.6) 2 (3.0) 4 (6.0) 7 (10.4)
ECOG PS, n (%) 0 / 1	31 (46.3) / 36 (53.7)
Median number of prior systemic therapy regimens (range) 1-2 3 4+	4.0 (1–10) 15 (22.4) 12 (17.9) 40 (59.7)
Site of metastases, n (%) Lung Liver Lymph node Peritoneal	58 (86.6) 47 (70.1) 27 (40.3) 19 (28.4)
RAS Mutation Status, n (%) RAS mutated RAS WT Unknown	46 (68.7) 10 (14.9) 11 (16.4)

- N = 67 MSS CRC patients were enrolled across Part 1a and Part 1b.
- Patients were heavily pre-treated with majority having received 4 or more lines of treatment.
- Most patients had high disease burden with multiple metastatic sites including liver and lung:
  - 70% rate of liver metastasis comparable to previous studies in CRC population.[1]

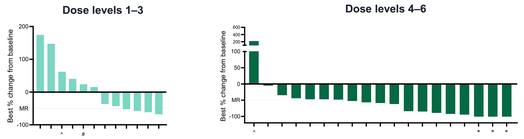
1. Yaeger R, et al. Efficacy and safety of adagrasib plus cetuximab in patients with colorectal cancer harboring KRAS G12C: results from the KRYSTAL-1 trial. *J Clin Oncol*. 2025;43(4_suppl):131. doi:10.1200/JCO.2025.43.4_suppl.131

Figure 5. Efficacy in MSS CRC: Investigator-determined RECIST 1.1 Response of Target Lesions



- The disease control rate in MSS CRC participants with at least one on-study scan at 8 weeks or later (N=34) was higher at dose levels 4–6 (11/22; 50%) compared to dose levels 1–3 (4/12; 33.3%).

Figure 6. ctDNA Response in CRC to FOG-001 Treatment by Dose Level: Increased rate of molecular responses (MR) observed at efficacious dose levels 4–6 (ctDNA test performed by Tempus)

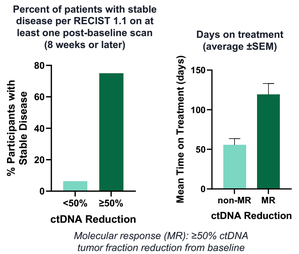


Patients with baseline plus at least 1 on-study ctDNA tumor fraction (TF) readout included (C2D1, C3D1, then every 2 cycles up to 1y); Baseline ctDNA TF<0.1% (LOB) not included;
*Baseline TF<0.25%; Biomarkers of note: #, WPAM negative; ^ TCF7L2(TCF4) loss of function

Background: ctDNA is a fraction of the cell free DNA. It is released by tumor lesions into circulating blood, and the quantity of ctDNA represents both the tumor volume and character; Deep ctDNA reduction (e.g., 50%, defined as molecular response) is associated with prolonged disease control and survival (Thompson, JCO Prec Oncol 2021; Guttar, SITC 2024; Maron, Clin Cancer Res 2019; Mitra, AACR 2024)

- Molecular response (MR) is defined as ≥50% reduction in ctDNA tumor fraction compared to baseline.
- In RECIST and ctDNA evaluable patients:
  - Dose levels 1–3 (4 of 12; 33%) achieved ctDNA molecular response.
  - Dose levels 4–6 (12 of 20; 60%) achieved ctDNA molecular response.

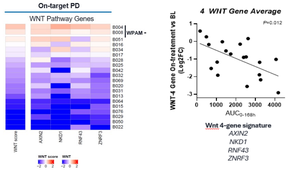
Figure 7. ctDNA Molecular Responses Correlate with Clinical Activity in MSS CRC



Molecular response (MR): ≥50% ctDNA tumor fraction reduction from baseline

- Participants with MR have a higher disease stabilization rate (75%) than those without MR (6.3%).
- Average time on treatment was longer for participants with MR (119.0 days) compared to those without MR (55.6 days).

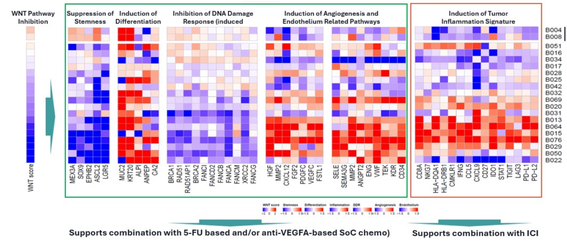
Figure 8. FOG-001 Demonstrates Exposure-Related Inhibition of WNT Signaling



PK data as of 27Jun2025; Tumor PD data as of 12Aug2025; N=19 patients with available PK data and paired tumor biopsy RNA seq data

- Clinical evidence of intratumoral target engagement by FOG-001 in MSS CRC.

Figure 9. FOG-001 Inhibition of WNT Signaling Provides Rationale for Combination Development: Part 1b MSS CRC paired tumor biopsies RNAseq (screening vs on-treatment (3–5 weeks post 1st dose))



Tumor PD data as of 12Aug2025; N=20 pts with paired tumor biopsy RNA seq data

Figure 10. Combination Cohorts in Ongoing FOG-001-101 Study (NCT05919264)

Key inclusion and exclusion criteria

Key inclusion criteria
- Aged 18 years or older
- ECOG PS score of 0–1
- Adequate organ and marrow function

Key exclusion criteria
- Bone metastasis
- Vertebral compression fracture or non-traumatic bone fracture in past 12 months and not receiving antiresorptive therapy
- Osteoporosis
- Inflammatory bowel disease
- Symptomatic brain metastases or leptomeningeal carcinomatosis

Monotherapy cohorts

FOG-001 monotherapy dose escalation; standard 3+3 design (solid tumor with WNT- pathway activating mutations (WPAMs) including Desmoid Tumors)

FOG-001 monotherapy dose escalation; standard 3+3 design (MSS CRC and WPAM+ solid tumors)

FOG-001 PD biomarker cohorts: patients with paired biopsies (MSS CRC; patients with WPAM– tumors are not eligible)

Combination cohorts

FOG-001 + FOLFOX + bevacizumab (1L MSS CRC)

FOG-001 + nivolumab (3L MSS CRC, with and without liver metastases)

FOG-001 + trifluridine/tipiracil + bevacizumab (3L MSS CRC)

NCT05919264

Distinct aspects of β-catenin biology drive multiple biologically rational FOG-001 combinations for MSS colorectal cancer

Poster Session C
Saturday, October 25,2025
12:30-4pm

Conclusions

- FOG-001 monotherapy is well tolerated with a manageable safety profile:
  - No Grade 4 or Grade 5 TRAEs; Grade 3 TRAEs were manageable with supportive treatment and dose holds.
  - No patients discontinued treatment due to TRAEs.
- FOG-001 is the first and only true Wnt/β-catenin inhibitor as evidenced by the on-target intratumoral pharmacodynamic effect and encouraging anti-tumor activity across a range of Wnt/β-catenin-driven tumors:
  - ORR: 43% in non-CRC WPAM+ solid tumors.
  - Disease control rate: 50% in efficacy-evaluable MSS CRC patients treated at efficacious dose range (dose levels 4–6).
  - Molecular responses at efficacious doses correlated with increased disease stabilization rates and time on treatment.
- Pharmacokinetic profile is favorable, with extensive distribution, dose-proportional exposure, and low inter-patient variability.
- FOG-001's biological and clinical impact supports:
  - Further exploration in non-CRC WPAM+ solid tumors with low mutational burden.
  - Ongoing expansion in desmoid tumors.
  - Evaluation in MSS CRC in combination with a) standard 5-FU based chemotherapy, b) anti-VEGF agent, and c) nivolumab.

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