# A phase 1/2 study of FOG-001, a first-in-class direct β-catenin:TCF inhibitor, in patients with colorectal cancer and other locally advanced or metastatic solid tumors

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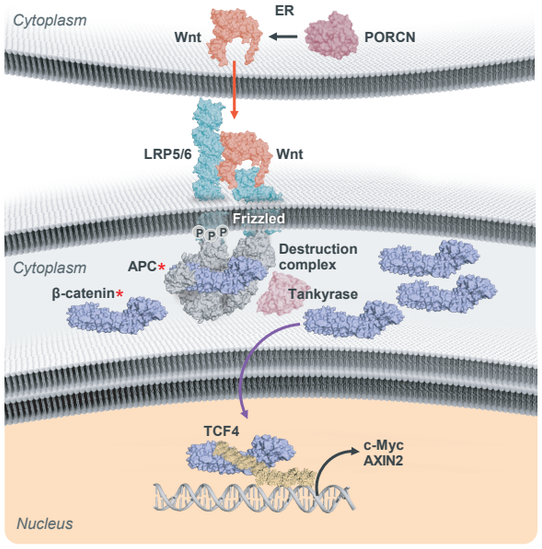
## Background

- Activating mutations in the Wnt/β-catenin pathway are found in 80–90% of CRCs, are often truncal, and are frequently observed in other Wnt pathway-dependent solid tumors, such as desmoid, adamantinomatous craniopharyngioma, and endometrial cancers.[1–7]
- Wnt/β-catenin pathway activation is associated with poor prognosis and resistance to chemotherapy and PD-1 inhibitors.[8–10] Development of agents targeting this pathway at the key β-catenin:TCF node has eluded the pharmaceutical industry to date.
- FOG-001 is a novel, synthetic, conformationally constrained α-helical peptide (Helicon) designed to bind to the β-catenin protein. FOG-001 potently and selectively disrupts the interaction of β-catenin with its obligate binding partner TCF4.
- Preclinical studies in PDX models of CRC and other WPAM+ solid tumors have shown that treatment with FOG-001 alone leads to potent tumor growth inhibition and regression.[11,12] Furthermore, combination with immune checkpoint inhibitors or standard-of-care therapies, including bevacizumab and 5-FU, had strong additivity/synergy in xenograft CRC models.
- In this poster we describe the design of FOG-001-101, a first-in-human phase 1/2 study of FOG-001 in patients with MSS CRC or advanced or metastatic solid tumors, including desmoid tumors, known to harbor a WPAM.

### FOG-001 targets the relevant downstream node in the Wnt/β-catenin pathway: The β-catenin:TCF4 interaction




*APC and β-catenin are the two most commonly mutated genes in the Wnt pathway.

### Longstanding and uniquely valuable target

- The Broad Institute's Cancer Dependency Map demonstrated **high tumor dependence** on the β-catenin:TCF4 interaction.
- All prior attempts to drug this pathway have been upstream of relevant mutations and **therefore not effective.**

### Precisely tailored mechanism

- FOG-001 potently and specifically **blocks TCF4 binding to β-catenin** competitively, while preserving other β-catenin complexes.
- Acts **downstream of key activating mutations of the Wnt pathway** (e.g. APC).

### Strong clinical and biological rationale for combination regimens

- Bevacizumab- and 5-FU-based combinations are the mainstays of first- and second-line treatment for patients with CRC. In MSS CRC PDX models:
  - FOG-001 + 5-FU had better antitumor activity versus either agent alone.
  - FOG-001 + bevacizumab had enhanced efficacy versus either agent alone.
  - Resistance to chemotherapy has been associated with pathway activation and stemness.
- Activation of the Wnt pathway can lead to immune exclusion and resistance to IO therapies:
  - Immunotherapy has not been shown to be active in MSS CRC, where the immunosuppressive Wnt pathway is almost universally activated.[10,13]
  - In other tumor types (e.g. NSCLC, melanoma, MSI-H CRC), where immunotherapy may be initially active, resistance may develop due to activation of the Wnt pathway.
  - Wnt pathway inhibition with FOG-001 has been proposed as a key mechanism to unlock anti-PD-1 treatment potential in patients with CRC in synergy with, or addition to, the inhibitory effect of FOG-001 on proliferation and survival.
  - FOG-001 potentiates response to PD-1 inhibitors, as demonstrated in MC38 *APC*$^{+/-}$ syngeneic tumors: β-catenin activation leads to beneficial FOG-001 efficacy in combination with anti-PD-1 antibodies versus FOG-001 or anti-PD-1 alone.

## FOG-001-101 Part 1 study design[a]

- FOG-001-101 is a phase 1/2, multicenter, open-label, non-randomized, dose-finding study of weekly IV FOG-001 alone and in combination with other medicines.
- The study consists of two parts: dose escalation (Part 1a and 1b) and dose expansion (Part 2).
- Part 1 will include a PD biomarker cohort (Part 1b) of patients with MSS CRC.
  - The effects of FOG-001 on key downstream components of the Wnt pathway, including expression of Myc as a representative biomarker of PD activity, will be evaluated in mandatory biopsy pairs.
  - Selection of Myc is based on preclinical findings in CRC PDX models with activated Wnt pathway, in which robust and consistent suppression of intratumoral PD markers, such as Myc, provides evidence of direct dose-related target engagement correlated with efficacy.
  - In particular, suppression of tumor Myc expression provides a potential basis for the antitumor effects of FOG-001, given the well-established role of Myc in β-catenin-driven tumorigenesis.

### 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**
(MSS CRC and WPAM+ solid tumors)

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

**FOG-001 monotherapy dose escalation; standard 3+3 design**
(desmoid tumors)

### 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)

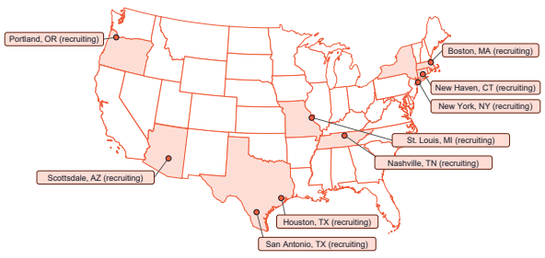
[a]Please refer to QR code for full eligibility criteria, objectives, and outcomes. Additional planned cohorts not currently enrolling are not shown.

### FOG-001-101 Part 1 study objectives and endpoints

| Study objectives | Outcomes measures |
|---|---|
| **Primary** | **Primary** |
| Safety and tolerability of FOG-001 (alone or in combination) to determine the MTD or maximum feasible dose | Treatment-emergent AEs (CTCAE v5.0), laboratory values, vital signs, ECGs, BMD, physical examinations |
| **Secondary** | **Secondary** |
| PK profile of FOG-001 and associated metabolite(s) to establish PK parameters | $C_{max}$, $T_{max}$, AUC, $C_{trough}$, $V_d$ (FOG-001 only), and CL (FOG-001 only) |
| Preliminary RP2D and dosing schedule | Based on AEs, PK, PD, evidence of clinical activity |
| Preliminary antitumor activity | ORR, BOR, DOR, DCR, TTP |

## Current status

- Part 1 is actively enrolling patients in the United States (NCT05919264).




## References

1. Zhan T, et al. Oncogene 2017;36:1461–73.
2. Polakis P. Cold Spring Harb Perspect Biol 2012;4:a008052.
3. Sebio A, et al. Expert Opin Ther Targets 2014;18:611–5.
4. Velho PI, et al. Eur Urol 2020;77:14–21.
5. Koushyar S, et al. Int J Mol Sci 2020;21:3927.
6. Harding JJ, et al. Clin Cancer Res 2019;25:2116–26.
7. Xu X, et al. Mol Cancer 2020;19:165.
8. Anastas JN, et al. Nat Rev Cancer 2013;13:11–26.
9. Matly A, et al. Crit Rev Oncol Hematol 2021;163:103337.
10. Grasso CS, et al. Cancer Discov 2018;8:730–49.
11. White BH, et al. Cancer Res 2023;83 (7_suppl):3094.
12. Si YG, et al. Cancer Res 2023;83(7_suppl):4972.
13. Bortolomeazzi M, et al. Gastroenterology 2021;161:1179–93.

## Abbreviations

1L, first line; 3L, third line; 5-FU, 5-fluorouracil; AE, adverse event; APC, adenomatous polyposis coli; AUC, area under the curve; AXIN2, axis inhibition protein 2; BMD, bone mineral density; BOR, best overall response; CL, clearance; $C_{max}$, maximum observed concentration; CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; $C_{trough}$, trough concentration; DCR, disease-control rate; DOR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; ER, endoplasmic reticulum; FOLFOX, folinic acid (leucovorin), fluorouracil, and oxaliplatin; IO, immuno-oncology; IV, intravenous; LRP5/6, lipoprotein receptor-related protein 5 or 6; MSI-H, microsatellite instability-high; MSS, microsatellite stable; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, pharmacodynamic; PD-1, programmed cell death protein-1; PDX, patient-derived xenograft; PK, pharmacokinetic; RP2D, recommended phase 2 dose; TCF, T-cell factor; TCF4, T-cell transcription factor 4; $T_{max}$, time to $C_{max}$; TTP, time to progression; $V_d$, volume of distribution; WPAM, activating mutations in the Wnt/β-catenin pathway.

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- For further information on this study, please scan the QR code:

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