Distinct Aspects of β-Catenin Biology Drive Multiple Biologically Rational FOG-001 Combinations for MSS Colorectal Cancer

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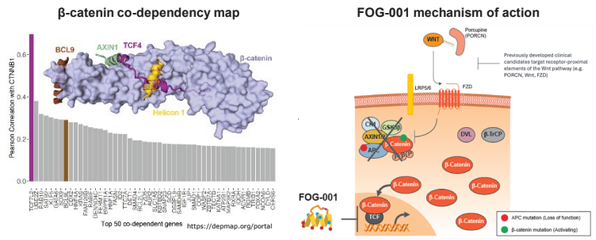
Background: β-catenin in Oncology

- **Prevalence**: Wnt pathway–activating mutations (WPAMs) occur in >80% of colorectal cancers and desmoid tumors, as well as a substantial subset of liver, gastric, and endometrial malignancies. These mutations disable the β-catenin degradation complex, driving constitutive activation of β-catenin and its nuclear accumulation.
- **Oncogenic function:** Nuclear β-catenin complexes with TCF/LEF transcription factors to induce gene programs essential for proliferation, survival, and malignant progression.
- **Therapeutic rationale:** Blocking the β-catenin–TCF4 interaction is a compelling strategy with potential impact across numerous Wnt-driven cancers.
- **Pathway effects:** Aberrant β-catenin signaling promotes VEGFR activation, dampens antitumor immune surveillance, confers reduced sensitivity to conventional therapeutics and enhances RAS signaling.
- **Clinical implications:** Given its central role in cancer stem cell maintenance, progression, and therapy resistance in colorectal cancer, co-targeting β-catenin with standard chemotherapies or immunotherapies may improve treatment efficacy by eradicating stem-like populations, reversing resistance networks, and enhancing immune infiltration.

Figure 1. Targeting the β-catenin:TCF interaction with the FOG-001 Helicon



RAS and WNT/β-catenin Crosstalk in Oncology

- Aberrant β-catenin and RAS signaling commonly co-occur in MSS CRC, driving reciprocal resistance to single-pathway therapies.
- **Reciprocal Bypass Resistance:** Nonclinical observations have highlighted that inhibition of oncogenic RAS signaling or suppression of WNT/β-catenin activity can lead to reciprocal elevation of the either pathway
- **Oncology Implications:** Reciprocal resistance mechanisms via β-catenin/RAS crosstalk underscore the need for combined or sequential inhibition strategies in Wnt- and RAS-driven cancers.

Figure 2: Mechanistic Interplay between RAS signaling and WNT/β-catenin activity

At transcriptional level, β-catenin/ TCF-driven gene expression promotes proliferation and survival, and RAS–ERK signaling further amplifies growth and tumor progression.

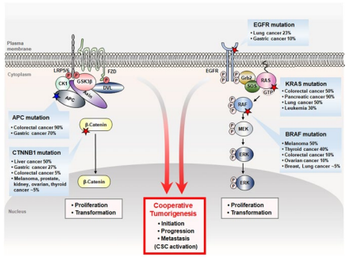


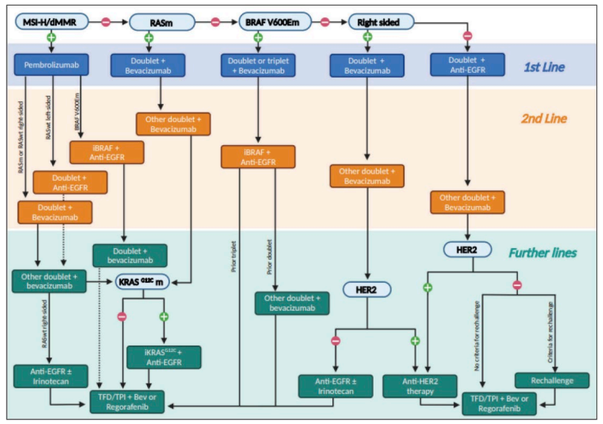
Figure3 from https://doi.org/10.1038/s41698-018-0049

Objectives

- Provide additional nonclinical data to aid the advancement of FOG-001 in patients with MSS CRC
- Evaluate nonclinical efficacy of FOG-001 together with a standard chemotherapeutic agent (5-FU), immune checkpoint inhibitor (anti-PD1), anti-VEGF and RAS pathway inhibitors.

Nonclinical evaluation of FOG-001 combinations across lines of treatment in mCRC

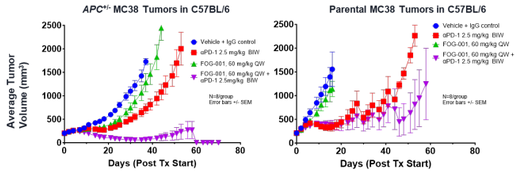
Figure 2. Treatment scenarios of unresectable mCRC in fit patients highlight multiple opportunities for combination with FOG-001



Notes: doublet (FOLFOX, CAPOX or FOLFIRI); triplet (FOLFOXIRI)
Ref: Figure 1, *ecancer 2023, 17:1544; www.ecancer.org; DOI: https://doi.org/10.3332/ecancer.2023.1544*

Nonclinical data supports the use of FOG-001 in combination with immune checkpoint inhibitors

Figure 3. β-catenin Activation (*APC*+/-) Leads to Beneficial FOG-001 Combination Efficacy with αPD-1 Ab



Treatment Group	Complete Response (CR)
Vehicle + IgG control	0/8
αPD-1	0/8
FOG-001	0/8
FOG-001+αPD1	**6/8**

Treatment Group	Complete Response (CR)
Vehicle + IgG control	0/8
αPD-1	0/8
FOG-001	0/8
FOG-001+αPD1	**2/8**

FOG-001 enhances antitumor efficacy in combination with anti–PD-1 therapy. FOG-001 (60 mg/kg QW) was tested with anti–PD-1 (12.5 mg/kg BIW) in APC$^{+/-}$ and parental MC38 tumor models. The combination enhanced antitumor activity and complete responses in 6/8 and 2/8 mice, respectively, versus no CRs with single agents. Data represent mean ± SEM (N=8 per group).

Nonclinical data supports the use of FOG-001 in combination with RAS signaling inhibitors

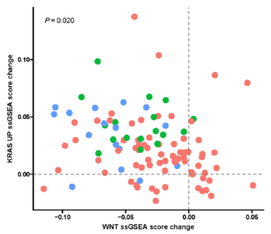


Figure 4. WNT suppression is associated with KRAS up-regulation in PDX models with response to FOG-001 (60 mg/kg). Scatterplot of WNT ssGSEA score change (x-axis) vs KRAS-UP ssGSEA score change (y-axis) across CRC PDX models treated with FOG-001 at 60 mg/kg. **Red dots** represent models with TGI < 80% (refractory), **Green dots** indicate stasis (80–100%), and **Blue dots** mark regressions (> 100%).
Resistant tumors cluster in the KRAS-up/WNT-neutral quadrant, whereas regressing and static models show down-modulation of both pathways.
A significant association (P = 0.020) supports that suppression of WNT and KRAS signaling correlates with antitumor response.

PDX Model	*KRAS* Allele	*APC* Mutation	*AXIN2* mRNA (% Reduction from Vehicle)	*DUSP6* mRNA (% Increase from Vehicle)	FOG-001 Single Agent (Tumor Growth Inhibition)	FOG-001 + Pan-RAS Inhibition (Tumor Growth Inhibition)
CRC-043	G12D	E1554_K1555fs	↓ 78%	↑ 18%	61-97% (n=3)	96%
CRC-1018		Q739fs/Q1459X	57%	19%	13-71% (n=3)	95%
CRC-022	G12C	L946fs/L1471fs	34%	81%	93%	116%
CRC-024		S1549X/P1693fs/ V1690fs/G1659fs /A1661fs	95%	71%	-38%	104%
CRC-058	G12V	E1554_K1555fs	86%	8%	53%	94%
CRC-060		R876*/Q1429*	20%	92%	90%	104%

Table 1. Summary of pathway modulation and antitumor efficacy of FOG-001 ± RMC-6236 across KRAS-mutant CRC PDX models. FOG-001 (60 mg/kg) demonstrated single-agent tumor growth inhibition (TGI) across APC- and KRAS-mutant colorectal cancer PDX models. FOG-001 monotherapy suppressed Wnt signaling (decreased *AXIN2* mRNA) and induced *DUSP6* mRNA expression, indicating MAPK pathway feedback activation. Combination with the pan-RAS inhibitor RMC-6236 (25 mg/kg) resulted in additive to regressive activity depending on model genotype.

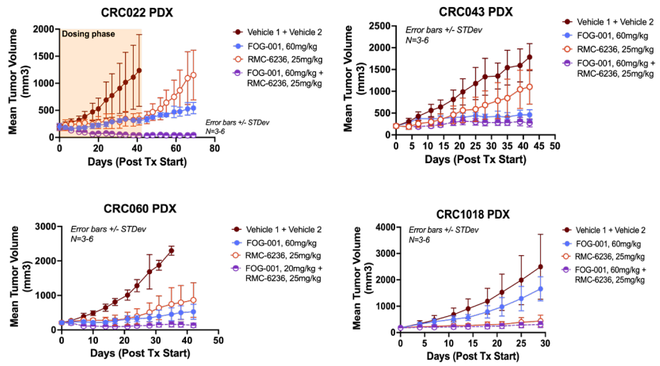


Figure 5. FOG-001 in combination with RMC-6236 enhances antitumor efficacy across KRAS-mutant CRC PDX models. Tumor volume data are shown for KRAS-mutant CRC PDX models treated with FOG-001 (60 mg/kg QW), RMC-6236 (25 mg/kg QD), or the combination. Additive efficacy was observed in G12D and G12V models, with tumor regressions in the G12C model (CRC022). In CRC022, treatment withdrawal following regression is being used to assess response durability off therapy. Error bars represent mean ± SD (N = 3–6 per group).

Nonclinical data supports the use of FOG-001 in combination with 1L and 2L standard of care

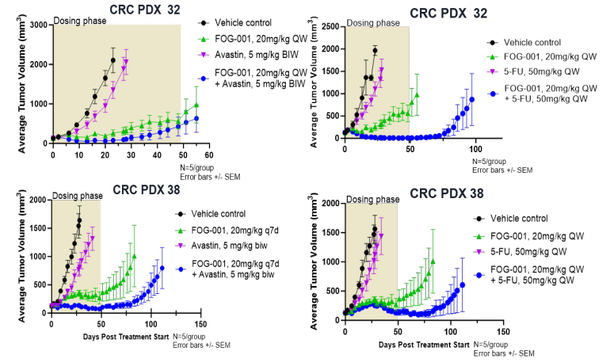


Figure 6. FOG-001 in combination with 1L and 2L standard-of-care agents enhances antitumor efficacy in KRAS-mutant CRC PDX models. FOG-001 (20 mg/kg QW) was evaluated alone or in combination with 5-FU (50 mg/kg QW) or bevacizumab (5 mg/kg BIW) across multiple KRAS-mutant CRC PDX models (CRC32 and CRC38). FOG-001 monotherapy produced measurable tumor growth inhibition, while combinations with either 5-FU or bevacizumab led to deeper and more durable regressions compared with single-agent treatment. These data support additive or greater-than-additive activity when FOG-001 is combined with established 1L and 2L MSS CRC treatment backbones. Tumor volume data represent mean ± SEM (N=5 per group).

Conclusions

- FOG-001, a selective β-catenin/TCF inhibitor, demonstrates broad activity across APC- and KRAS-mutant MSS CRC PDX models.
- Combinations with standard-of-care agents (5-FU and anti-VEGF) enhance tumor growth inhibition, supporting potential integration with existing treatment backbones.
- FOG-001 plus immune checkpoint inhibitors increases response depth and durability, consistent with relief of Wnt-driven immune exclusion.
- Combination with pan-RAS inhibition (RMC-6236) drives additive to regressive activity across KRAS genotypes and deepens responses in G12C and G12V models.
- Mechanistic and PD data confirm Wnt suppression (*AXIN2*↓) and mitigation of MAPK feedback (*DUSP6*↑), supporting complementary pathway targeting.
- Collectively, these findings support the translational potential of FOG-001 combinations to deepen and extend responses across RAS-driven MSS CRC settings.

References

1. Jeong, WJ., Ro, E.J. & Choi, KY. Interaction between Wnt/β-catenin and RAS-ERK pathways and an anti-cancer strategy via degradations of β-catenin and RAS by targeting the Wnt/β-catenin pathway. npj Precision Onc 2, 5 (2018). https://doi.org/10.1038/s41698-018-0049

2. *ecancer 2023, 17:1544; www.ecancer.org; DOI:https://doi.org/10.3332/ecancer.2023.1544*

Acknowledgments

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Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Boston, MA, USA, October 22-26, 2025.