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Symbiotic-GI-03: a randomized, double-blind, phase 3 study of first-line PF-08634404, a PD-1/VEGF bispecific antibody, in combination with mFOLFOX6 in patients with metastatic colorectal cancer (mCRC)

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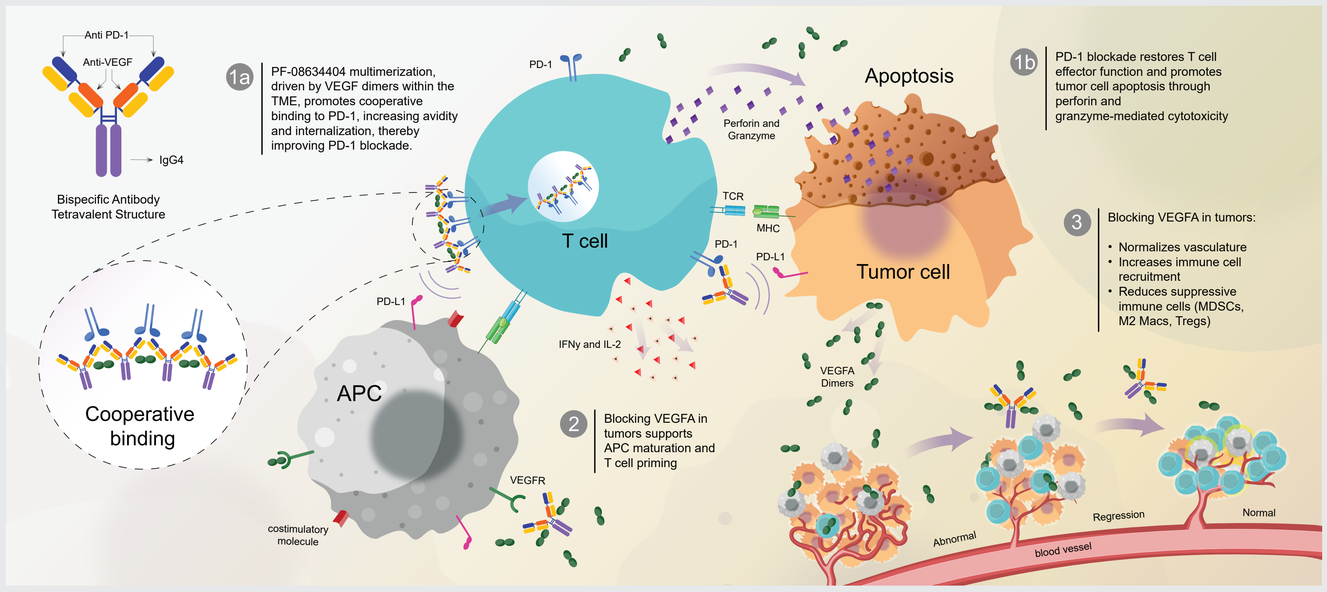
Background

- Multi-agent chemotherapy regimens ± anti-VEGF or anti-EGFR agents are currently the SOC for patients with mCRC without targetable mutations.[1] However, the 5-year survival rate remains low at approximately 16%[2]
- Despite efficacy in solid tumors, monotherapy with ICIs, such as PD-1 inhibitors, has shown limited activity in pMMR/MSS mCRC, which represents ≈95% of mCRC.[3,4] Combining ICIs with biological therapies (eg, anti-VEGF monoclonals), and/or chemotherapy has demonstrated potential synergistic antitumor effects in solid tumors, including mCRC, warranting further investigation in pMMR/MSS mCRC[5]
- Simultaneous bispecific targeting of PD-1 and VEGF in conjunction with chemotherapy may enhance antitumor activity by boosting T-cell activation via improved PD-1 blockade and by normalizing vasculature and increasing immune function via blocking VEGF-A
- PF-08634404 is a fully human IgG4 bispecific antibody targeting PD-1 and VEGF (**Figure 1**) that demonstrates stronger VEGF-A binding and inhibition relative to bevacizumab and ivonescimab[6-9]
- A phase 2 study of PF-08634404 with mFOLFOX6 or XELOX demonstrated promising antitumor activity with a manageable safety profile in 1L treatment of mCRC[9]
- Results from this phase 2 study support initiation of Symbiotic-GI-03, a phase 3 study of 1L PF-08634404 + mFOLFOX6 versus bevacizumab + mFOLFOX6 in patients with mCRC (NCT07222800)

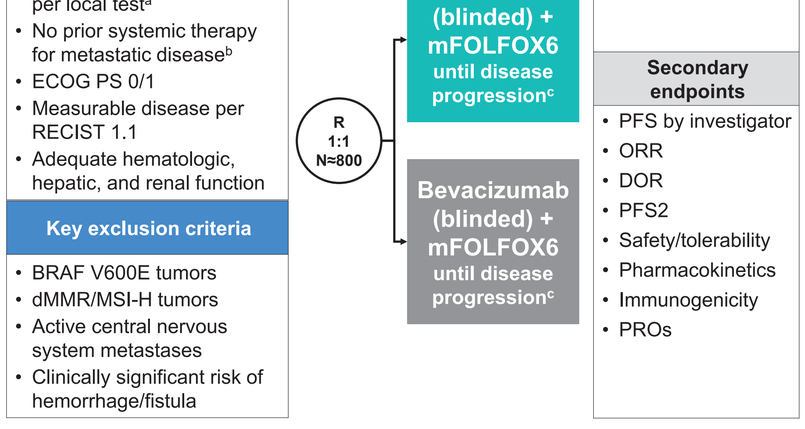
Figure 1. Proposed mechanism of action of PF-08634404, a bispecific antibody targeting PD-1 and VEGF



Study Design

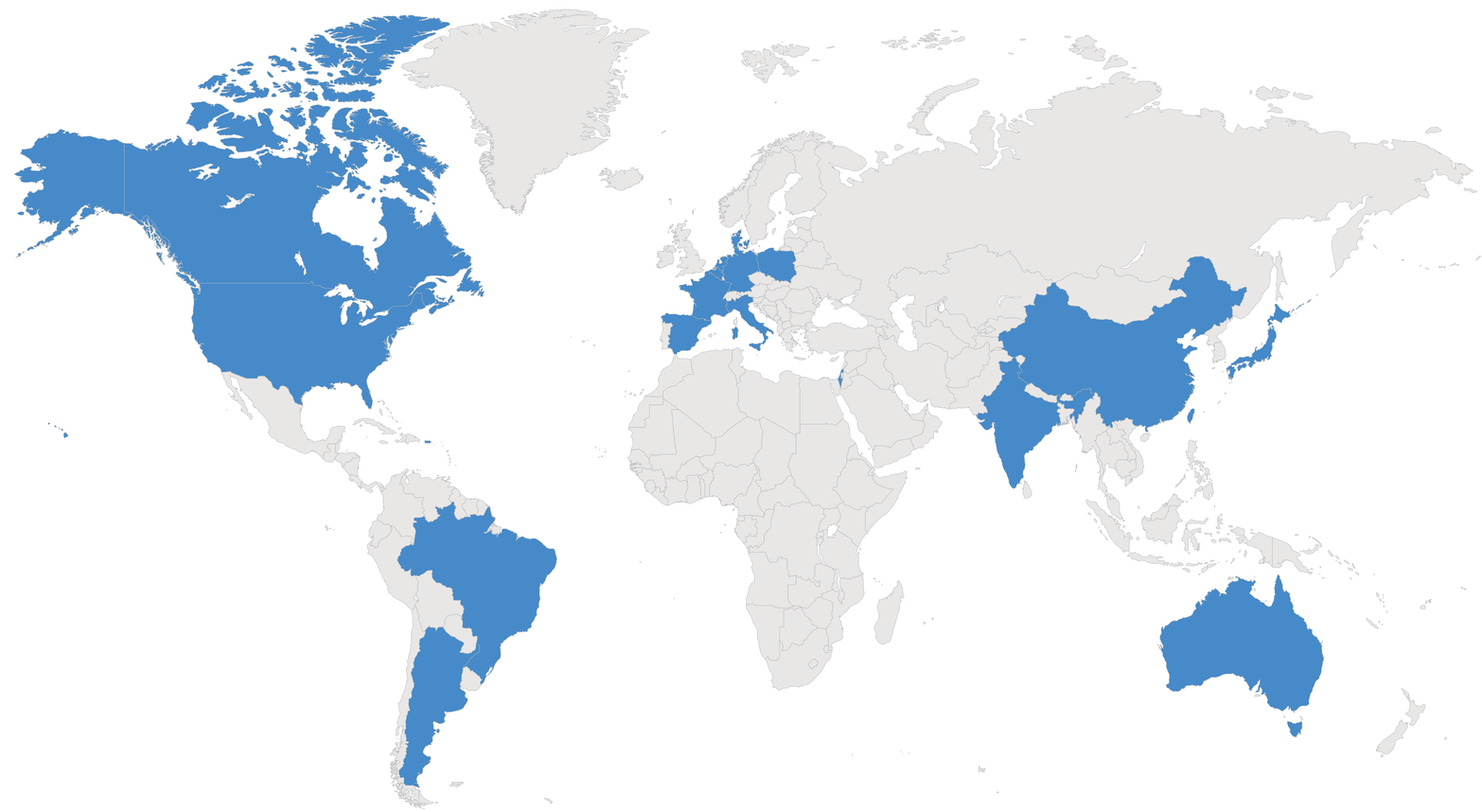
- Symbiotic-GI-03 (**Figure 2**) is a randomized, double-blind, phase 3 study in adults with previously untreated mCRC
- Patients will be randomized 1:1 to 2 arms:
  - PF-08634404 + mFOLFOX6
  - Bevacizumab + mFOLFOX6
- Randomization will be stratified by:
  - Regions (North America vs Europe vs rest of world)
  - *RAS* status (mutant vs wild-type)
  - Liver metastasis per investigator (yes vs no)
- Study endpoints are described in **Figure 2**
- Enrollment is active (**Figure 3**)

Figure 2. Symbiotic-GI-03 study design



[a]Patients with unknown *RAS* status despite attempt to test are eligible for participation. [b]Patients with early-stage disease who received prior systemic neoadjuvant or adjuvant chemotherapy and present with reoccurrence/metastatic disease within 6 months of stopping treatment will count as having prior therapy in the metastatic setting and are not eligible. [c]Until progressive disease confirmed by BICR, or unacceptable toxicity, withdrawal of consent, or death.

Figure 3. Countries and regions with active study sites



Countries and regions with active study sites

Asia-Pacific/rest of world
- Australia
- China
- India
- Israel
- Japan
- Taiwan

Europe
- Belgium
- Denmark
- France
- Germany
- Italy
- Poland
- Netherlands
- Spain

South America
- Argentina
- Brazil

North America
- Canada
- United States/Puerto Rico

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Abbreviations

1L, first line; APC, antigen-presenting cell; BICR, blinded independent central review; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IgG4, immunoglobulin G4; IFN-γ, interferon-gamma; IL-2, interleukin-2; M2 Macs, M2 macrophages; mCRC, metastatic colorectal cancer; MHC, major histocompatibility complex; MDSC, myeloid-derived suppressor cells; mFOLFOX6, leucovorin, fluorouracil, and oxaliplatin; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD-1, programmed death-1; PFS2, progression after next-line therapy; pMMR, mismatch repair proficient; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; TCR, T-cell receptor; TME, tumor microenvironment; Tregs, regulatory T-cells; VEGF, vascular endothelial growth factor; XELOX, capecitabine and oxaliplatin.

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Disclosures/COIs

Cathy Eng reports a consulting role at Bayer, Boston Scientific, GlaxoSmithKline, HalioDx, Merck, Mirati, Hookipa, J&J, Natera, Roche, Seagen, Taiho, and Veloxis and receives research funding (to VUMC) from Elevar, Hutchinson, Merck, and Pfizer.

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