### Title

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# A Phase 1 Study of Cabozantinib and Trifluridine/Tipiracil in Metastatic Colorectal Adenocarcinoma

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## Abstract

The purpose of this phase I trial was to determine the recommended phase II dose for the combination of cabozantinib and trifluridine/tipiracil in 15 patients with colorectal cancer. The results demonstrate that the combination of both drugs is tolerable with the use of prophylactic growth factors. The observed preliminary efficacy warrants further evaluation.

**Introduction:** This study determined the safety and recommended phase 2 dose (RP2D) of the multikinase inhibitor cabozantinib in combination with trifluridine/tipiracil (FTD/TPI) in refractory metastatic colorectal carcinoma (mCRC).

**Patients and Methods:** Single institution investigator-initiated phase 1 study using 3+3 design. Eligible mCRC patients had received prior standard regimens. Cabozantinib was given orally (p.o.) at 20 mg (dose level [DL] 0) or 40 mg (DL 1) daily on days 1–28, and FTD/TPI p.o. at 35 mg/m$^2$ on days 1–5 and 8–12 every 28 days. Prophylactic growth-factor support was allowed.

**Results:** Fifteen patients were enrolled. Median age 56 years (31–80), male (12/15), ECOG 0/1 = 9/6. Three patients were treated at DL 0 and another nine were treated at DL 1, none exhibiting a DLT. Most common any grade (G) treatment related adverse events (TRAE) were diarrhea (50%), nausea (42%), neutropenia (42%), fatigue (33%), and rash (25%). G3–4 TRAE were neutropenia (25%) and thrombocytopenia, hypokalemia, and weight loss (each 8%). No serious TRAE or G5 were reported. The RP2D was determined to be DL 1. Median PFS was 3.8 months (95% CI 1.9–6.8) and disease control rate was 86.7%.

**Conclusion:** The combination of cabozantinib and FTD/TPI is feasible and tolerable at standard doses with the use of growth factors and showed encouraging clinical activity in refractory mCRC.

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Authors' Contributions

F.D. designed the study. F.D., J.B., J.V., M.J.K., J.A.Z., and M.T.C. collected the data. F.D., J.B., and T.H.T. analyzed the data. All authors wrote the manuscript.

Ethics Approval and Consent to Participate

The trial was approved by the Institutional Review Board at the University of California Irvine (UCI 20–134) and adhered to good clinical practice guidelines. All patients provided written, informed consent as a condition of study participation. The study was performed in accordance with the Declaration of Helsinki.

**ClinicalTrials.Gov:** NCT04868773.

### Keywords

Angiogenesis; Axl; cMET; Recommended phase II dose; Resistance

## Introduction

The prognosis for patients with advanced metastatic colorectal adenocarcinoma (mCRC) remains poor, with a 5-year overall survival of 14.7%.[1] Trifluridine and tipiracil (FTD/TPI) is an orally active, antimetabolite agent comprised of trifluridine, a thymidine-based nucleoside analogue, and tipiracil, a potent thymidine phosphorylase inhibitor.[2] Single agent FTD/TPI improved median overall survival (mOS) in refractory mCRC by 1.8 months versus placebo.[3] In a randomized phase II trial, the addition of bevacizumab to FTD/TPI in refractory mCRC led to an improved progression-free survival (PFS) in the combination versus FTD/TPI alone (HR = 0.45).[4] The impact on mOS was recently demonstrated in the phase III randomized SUNLIGHT trial (HR for mOS = 0.61).[5]

Cabozantinib is a potent inhibitor of three principal targets: VEGFR, cMET, and Axl.[6]

Dysregulation of the hepatocyte growth factor (HGF)/MET pathway is associated with poor prognosis, more aggressive biological characteristics of the tumor, and shorter survival in mCRC.[7,8] A meta-analysis for OS based on cMET status showed high cMET expression is associated with poor prognosis in CRC.[9] Case series confirm high cMET expression predicts worse survival.[9] Furthermore, dysregulated HGF/MET signaling is associated with poor prognosis and resistance to VEGF inhibition in mCRC.[10] *In vitro*, Axl is an oncotarget in human colorectal cancer[11] and promotes migration and invasion.[12] Axl is also prognostic in patients with mCRC.[13]

We hypothesized that the combination of cabozantinib with FTD/TPI is tolerable and might improve outcomes in mCRC, via targeting of both angiogenesis and other crucial signaling pathways. Thus, we conducted a phase I study to determine the recommended phase 2 dose (RP2D) of cabozantinib and FTD/TPI in patients with mCRC.

## Methods

### Study Design and Patients

This was a single institution, phase 1 clinical trial performed at the University of California Irvine. Patients had histologically or cytologically confirmed colorectal adenocarcinoma, which was locally advanced, recurrent, or metastatic and not amenable to curative intent surgery. Patients had progressed or not tolerated, a regimen of fluoropyrimidine, irinotecan, oxaliplatin, and cetuximab or panitumumab (if appropriate). Prior exposure to bevacizumab or ramucirumab was allowed. Patients who had exhausted all other standard of care options were also eligible.

Patients were ≥18 years old, with an ECOG performance status of 0–2, and a life expectancy greater than 3 months based on investigator's assessment. Patients who had major surgery

within four weeks, or chemotherapy or radiotherapy within two weeks prior to entering the study, as well as those with prior treatment with cabozantinib, and those with known brain metastases were excluded. Presence of measurable disease by RECIST 1.1 was not mandatory. The trial was approved by the Institutional Review Board at the University of California Irvine (UCI 20–134) and adhered to good clinical practice guidelines. All patients provided written, informed consent as a condition of study participation. The study was first registered at Clinicaltrials.gov on 03/05/2021 (NCT04868773).

## Procedures

Dose escalation was performed based on standard "3 + 3" rules.[14] The starting dose level (0) was FTD/TPI 35 mg/m$^2$ p.o. twice daily on days 1–5 and 8–12, and cabozantinib 20 mg p.o. once daily on days 1–28. Dose level (1) was FTD/TPI 35 mg/m$^2$ p.o. twice daily on days 1–5 and 8–12, and cabozantinib 40 mg p.o. once daily on days 1–28. Within the protocol there was also a dose level (−1) with FTD/TPI 25 mg/m$^2$ and cabozantnib 20 mg p.o. daily. However, no patients required treatment on dose level (−1). For all dose levels, prophylactic growth factor support with peg-gcsf 6 mg s.c. was administered on day 13 of each cycle. The cycle duration was 28 days. If grade 3 thrombocytopenia was observed at the beginning of cycle 2 or later, romiplostin 2–3 μg/kg (per investigator discretion) was administered once a week until a platelet count ≥ 80,000/mcl was achieved, and then on day 13 and 19 of each subsequent cycle. Dose escalation did not occur until three DLT evaluable patients had been observed for the entire DLT period (cycle 1, day 28).

All patients who received treatment on this protocol were evaluable for toxicity. We assessed toxicity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.[15] After the DLT period, subsequent treatment delays up to 4 weeks were allowed due to intolerable toxicities (grade > 1) per investigator discretion. Imaging studies were performed on protocol schedule regardless of treatment delays.

Treatment continued on protocol until disease progression defined as radiographic progression by RECIST v1.1 criteria,[16] death or symptomatic progression as clinically determined by the treating physician, unacceptable toxicity, or withdrawal of consent. Radiographic tumor assessments using computed tomography (CT) of the chest, abdomen, and pelvis were performed at baseline and every 8 weeks, thereafter, for the duration of study participation. Magnetic resonance imaging of the abdomen and pelvis was permitted instead of CT scan based on the investigator's discretion. Tumor marker CEA (carcinoembryonic antigen) was measured prior to each cycle in patients with elevated baseline values.

## Outcomes

The primary endpoint was dose limiting toxicity (DLT) up to day 28 of cycle 1 (ie, DLT period). DLT was defined as the presence of any grade 3 or higher nonhematological or grade 4 or higher hematological toxicity at least possibly related to treatment within the DLT assessment window.[17] The secondary endpoints were best objective response rate by RECIST v1.1 in patients with measurable disease, median progression-free (PFS) and

overall survival (OS). PFS was defined as time from start of treatment to progression or death, and OS was defined as time from start of treatment to death.

### Statistical Analysis

The RPD2 was defined as the highest dose level at which ≤ 1 patient among the first six evaluable patients experienced a DLT. Evaluable was defined as patient completed the 28-day DLT period. Patients who did not complete the DLT period for reasons other than toxicity were replaced. Therefore, at least nine and up to 15 evaluable patients were required to determine the DLT. If no DLTs were observed in the study, expansion of the DL 1 cohort by up to 12 patients was allowed to improve precision of the estimate of efficacy.

## Results

### Patient Characteristics

Between August 2021 and May 2022, 19 patients consented to the study. Two patients withdrew consent and two patients were not eligible, and thus, 15 patients started the study treatment. Table 1 shows the patient and disease characteristics. Twelve patients were male (80%), median age was 56 years (range 31–80), 66% were Caucasian, 27% were Hispanic, and 7% Asian. One-third (5 of 15) had de novo unresectable advanced disease with the primary tumor in place. All tumors were microsatellite stable and 40% were right sided. The most common sites of metastases included liver and lung (each n = 10) and 40% (n = 6) had three or more sites of metastases (including six patients with peritoneal carcinomatosis). Median lines of prior treatment were two (maximum = 4). All patients had received prior fluoropyrimidine and oxaliplatin and the majority had also received irinotecan and anti-VGF directed therapy (93.3% and 86.7%, respectively). At the time of data cut-off (26 December 2022), four patients remain on treatment. The main reason for treatment discontinuation was disease progression.

### Adverse Events

All patients who started treatment were evaluated for DLT. Three patients were assigned to dose level (0). Since no DLT was observed, the remaining twelve patients were treated with dose level (1): cabozantinib 40 mg p.o. daily and FTD/TPI 35 mg/m$^2$ p.o. bid on days 1–5 and 8–12, every 28 days. Table 2 shows treatment-related adverse events (TRAE). All patients reported at least one TRAE; however, no grade 4 or higher TRAE was observed. The most common grade TRAEs were nausea and diarrhea (each n = 7, 47%), followed by fatigue (n = 6, 40%) and neutropenia (n = 5, 33%). Three patients experienced grade 3 TRAEs: neutropenia (n = 1), thrombocytopenia (n = 1), weight loss and hypokalemia (n = 1, same patient). All grade 3 events occurred outside of the DLT period. There were no grade 5 adverse events.

### Dose Delivery

A dose reduction due to TRAE attributed to FTD/TPI occurred in two patients. One patient experienced grade 3 thrombocytopenia after the DLT period and had one dose reduction of FTD/TPI. The second patient had two dose reductions of FTD/TPI. The first dose reduction for weight loss, the second dose reduction for diarrhea. Due to grade 2 diarrhea,

cabozantinib was dose reduced in the same patient as well. While all patients received g-csf support, two patients required additional growth factor support with romiplostim for thrombocytopenia (both occurred after DLT period).

### Efficacy

Median progression-free survival (Figure 1) and overall survival (Figure 2) were 3.8 (95% CI, 1.9–6.8) and 6.7 months (95% CI, 2.2-not evaluable), respectively. The PFS at 6 months was 28.9% (95% CI, 8.9–52.8). In all seven patients with measurable disease, the best objective response was stable disease. No patient had a partial response or better by RECIST v1.1 criteria. However, six patients had tumor reduction with a median best change of 14.3% (range: 8.9%−22.6%) and one patient had tumor growth as best response. In patients with tumor reduction, median time to nadir was 8 weeks (range: 8–16 weeks). Six of eight patients with no measurable disease at baseline remained on treatment for more than 8 weeks and two patients clinically progressed before the first on-treatment imaging at 8 weeks. Hence, in all 15 patients, the rate of disease control was 86.7% (13/15). Of fourteen patients with elevated CEA levels at baseline, six showed a decline in CEA (6/14 = 42.8%; median decline from baseline: 55%, range 34%−88%).

## Discussion

To our knowledge this is the first phase I clinical trial to show the feasibility of the combination of cabozantinib with a chemotherapy regimen in gastrointestinal cancers. One previous phase I trial attempted to combine cabozantinib with gemcitabine, however, an MTD could not be established due to DLT at low doses.[18] None of the 15 patients enrolled in the current study experienced a DLT. We were able to reach the maximum planned dose level (1) and expand the dose level (1) by another nine patients for a total of 15 evaluable patients.

While in the previous phase I study, the combination of cabozantinib with gemcitabine led to grade 3 ALT/AST elevations and thrombocytopenia, the most common treatment related adverse events in our study were nausea, diarrhea, and neutropenia. Based on the previous experience we had mandated prophylactic growth factors to be given on day 13 of the 28-day cycle. This likely contributed to patients being able to maintain treatment and avoiding grade 3 or higher neutropenia in all except for one patient. Additionally, based on the previous reports of thrombocytopenia as DLT, we had allowed for the addition of romiplostim support for chemotherapy induced thrombocytopenia. This was necessary for two patients. Overall, the observed major treatment related adverse events were treatable and or preventable, ie, with antiemetics and growth factors.

The importance of continued inhibition of the VEGF pathway in the treatment of mCRC has been confirmed across several lines of treatment as noted above. The addition of bevacizumab to FTD/TPI improved progression free survival initially in a phase II trial and more recently also overall survival in the phase III SUNLIGHT trial. The question is whether there is still a role for the continued development of cabozantinib with FTD/TPI given the recent results with the SUNLIGHT trial. In other diseases, two of the targets of cabozantinib, namely Met and Axl, have been shown to be implicated in overcoming

resistance to VEGF inhibitors in the treatment of solid tumors.[19] Hence, one could envision that cabozantinib as a multi tyrosine kinase inhibitor of Met, Axl, and VEGFR might have either additional benefits over a pure VEGF inhibitor such as bevacizumab or potentially overcome resistance in patients who are initially treated with FTD/TPI and bevacizumab. This needs to be explored in future studies.

It is challenging to compare PFS and OS between this study and the SUNLIGHT trial. This is partly due to a small sample size in our early phase trial. But there are also other important differences. While the SUNLIGHT trial mandated only two lines of prior treatment, our patient population is more heavily pretreated, with up to four lines of prior treatment. Additionally, our trial did not exclude prior treatment with regorafenib or even single agent FTD/TPI. Forty percent of the patients enrolled in our study had peritoneal carcinomatosis, which portends a poor prognosis in gastrointestinal cancers.[20] This study confirmed that objective response rate (ORR) with FTD/TPI regimens is low (the ORR in the SUNLIGHT trial was 6.3%). Among 15 patients enrolled in the current study, there were no objective responses by RECIST criteria. However, assuming the true rate is approximately 5%−6%, it is possible that we didn't see a response due to chance. Importantly, the disease control rate was almost 87% in our study, ie, numerically similar to FTD/TPI plus bevacizumab (76.6%) and higher than FTD/TPI alone (47.0%) as reported in the SUNLIGHT trial.

## Conclusion

The combination of cabozantinib (40 mg daily) and FTD/TPI (35 mg/m$^2$ on days 1–5 and 8–12) every 28 days is feasible and tolerable with encouraging clinical activity in refractory mCRC.

## Acknowledgments

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### Disclosure

FD has received research grants (to the institution) from AstraZeneca, Bristol-Myers Squibb, Merck, Genentech/Roche, Taiho, Exelixis, Trishula, Leap Therapeutics, has received a speaker honorarium from Amgen, Eisai, Ipsen, Exelixis, Sirtex, Deciphera, Ipsen, Natera, and has received a consultancy honorarium from Natera, QED, Eisai, Exelixis, Genentech/Roche. MTC has received research grants (to the institution) from Bristol-Myers Squibb, a speaker honorarium from Pfizer, Natera, Taiho, BMS, AstraZeneca, a consultancy honorarium from Amgen, Incyte, Eisai, Ipsen, Astellas, Taiho, Exelixis, QED, I-Mab, Tempus, Seattle Genetics, HelioDx, Bayer, AstraZeneca, Genentech/Roche, Pfizer, Natera, Taiho, BMS, Basilea. JAZ has received a consultancy honorarium from Tempus and Exact Sciences, has received research grants (to the institution) from Halozyme and Merck. JV has received a consultancy honorarium from Astrazeneca. The other authors declare that they have no conflict of interest.

## Data Availability

**Data Sharing Statement**

| **Article Info** | **n/a (editor will fill in this)** | |
|---|---|---|
| **Item** | **Question** | **Authors' Response (place "-" if not applicable)** |
| 1 | Would you like to share data collected for your study to others? | yes |
| 2 | If not, would you like to share the reason for your decision? | - |
| 3 | What data in particular will be shared? | All of individual collected data, after deidentified. |
| 4 | Any other documents will be share? Such as study protocol, statistical analysis plan, informed consent form, clinical study report, analytic code. | - |
| 5 | When will data availability begin? | Immediately starting publication |
| 6 | When will data availability end? | 1 year following article publication |
| 7 | To whom will you share the data? | Investigators who provide a methodologically sound proposal and whose proposed use has been approved by an independent review committee |
| 8 | For what type of analysis or purpose? | To achieve aims in approved proposal |
| 9 | How or where can the data/documents be obtained? | Proposals should be submitted via email to the corresponding author (FD) up to 12 months following article publication. To gain access, requestor needs to sign a data access agreement. |
| 10 | Any other restrictions? | - |

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### Clinical Practice Points

- The prognosis of advanced metastatic colorectal cancer (mCRC) remains poor. The addition of bevacizumab to trifluridine and tipiracil (FTD/TPI) in the salvage setting improves survival. However, primary or secondary resistance is common and additional treatment options are needed.
- The hypothesis of this trial was that the addition of cabozantinib to FTD/TPI, via cotargeting of cMET, Axl, and VEGFR is feasible and might improve outcomes in mCRC. The study objective was met. The recommended phase II dose was determined to be cabozantinib (40 mg daily) and FTD/TPI (35 $mg/m^2$ on days 1–5 and 8–12) every 28 days. The observed median PFS and OS were 3.8 and 6.7 months, respectively, and encouraging in this heavily pretreated population.

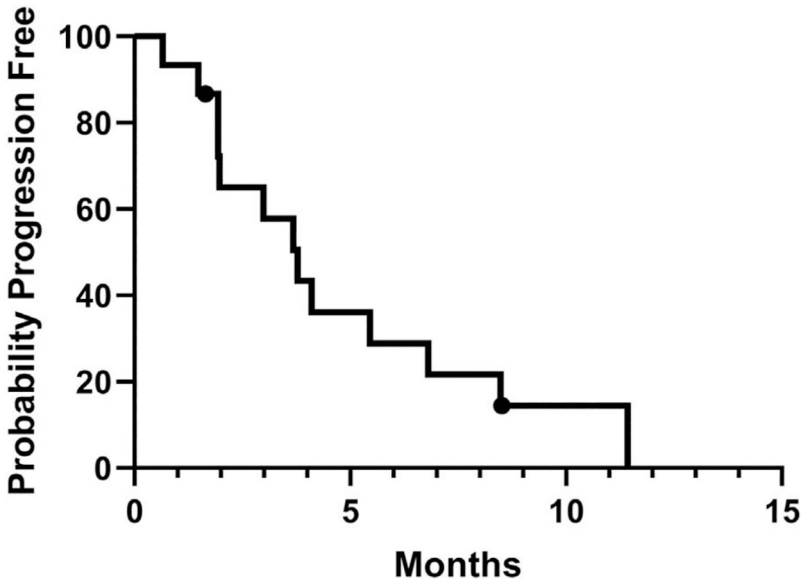


**Figure 1.**
Progression-free survival.

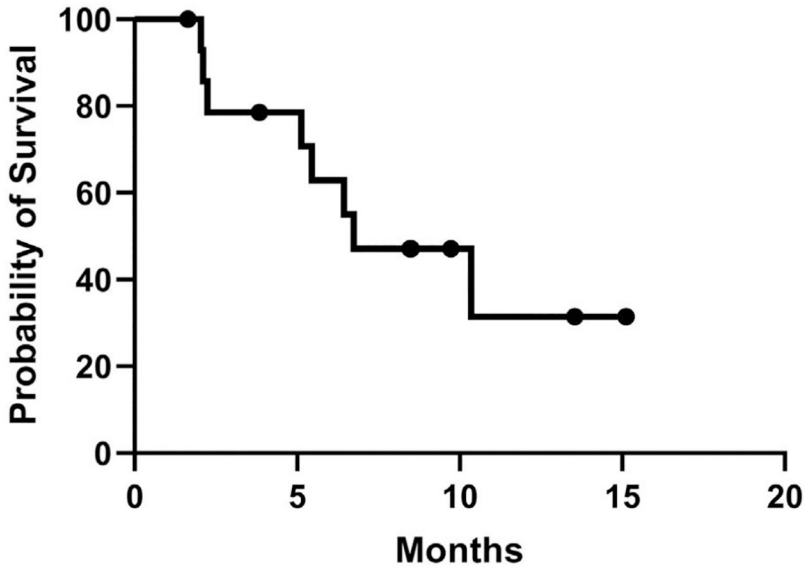


**Figure 2.**
Overall survival.

## Table 1

Patient Baseline Characteristics

| | |
|---|---|
| **Total Patients, N (%)** | **15 (100)** |
| Age, years | |
| Median | 56 |
| Range | 31–80 |
| Gender, N (%) | |
| Male | 12 (80) |
| Female | 3 (20) |
| Ethnicity, N (%) | |
| Caucasian | 10 (67) |
| Hispanic | 4 (27) |
| Asian | 1 (7) |
| ECOG performance status, N (%) | |
| 0 | 9 (60) |
| 1 | 6 (40) |
| Tumor sidedness, N (%) | |
| Right | 6 (40) |
| Left | 9 (60) |
| Primary tumor resected, N (%) | |
| Yes | 10 (66.7) |
| No | 5 (33.3) |
| Mutation present, N (%) | |
| KRAS/NRAS | 9 (60) |
| BRAF | 3 (20) |
| None | 3 (20) |
| CEA level at baseline, ng/mL | |
| Median | 24 |
| Range | 1.4–580.1 |
| Mismatch repair, N (%) | |
| Proficient | 15 (100) |
| Deficient | 0 (0) |
| Site of metastases, N (%) | |
| Liver | 10 (66.7) |
| Lung | 10 (66.7) |
| Peritoneum | 6 (40) |
| Other | 8 (53.3) |
| Number of prior systemic treatments, N (%) | |
| Median | 2 |
| Range | 1–4 |
| Type of prior systemic treatments, N (%) | |
| Fluoropyrimidine | 15 (100) |

| **Total Patients, N (%)** | **15 (100)** |
|---|---|
| Oxaliplatin | 15 (100) |
| Irinotecan | 14 (93.3) |
| Anti-VEGF | 13 (86.7) |
| Anti-EGFR | 5 (33.3) |
| Other | 7 (46.7) |

**Table 2**

Treatment Related Adverse Events (TRAE)

| TRAE | Any Grade (%) | Grade 3 (%) |
|---|---|---|
| Nausea | 7 (47) | |
| Diarrhea | 7 (47) | |
| Fatigue | 6 (40) | |
| Neutropenia | 5 (33) | 1 (7) |
| Rash | 3 (20) | |
| Anorexia | 3 (20) | |
| Anemia | 3 (20) | |
| Thrombocytopenia | 2 (13) | 1 (7) |
| Mucositis | 2 (13) | |
| Hypertension | 2 (13) | |
| Edema | 1 (7) | |
| Abdominal Pain | 1 (7) | |
| Weight Loss | 1 (7) | 1 (7)[a] |
| Hypokalemia | 1 (7) | 1 (7)[a] |
| Hypophosphatemia | 1 (7) | |
| Constipation | 1 (7) | |

[a]Same patient.