Open-label Phase III Study of Arfolitixorin vs Leucovorin in Modified FOLFOX-6 for First-line Treatment of Metastatic Colorectal Cancer: AGENT

https://colorectalcanceragent.com/

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BACKGROUND

Current standard treatment for metastatic colorectal cancer (mCRC) in first-line consists of cytotoxic chemotherapy, combined with biologics such as bevacizumab, cetuximab, and panitumumab.[1] 5-fluorouracil (5-FU) in combination with the folate leucovorin is an established cornerstone of mCRC treatment.[1] 5-FU is converted to 5-fluorodeoxyuridine monophosphate (FdUMP), which potently inhibits the thymidylate synthase enzyme, consequently disrupting DNA synthesis and repair and leading to cell death in rapidly proliferating tumor cells **(Figure 1a)**.[2]

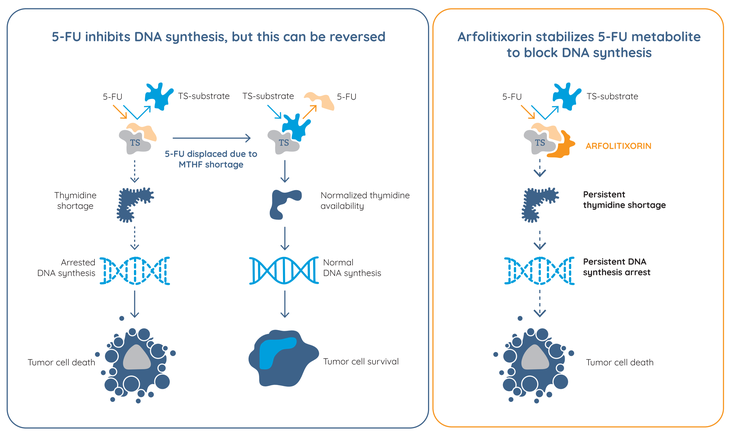
For effective 5-FU inhibition of thymidylate synthase, folates are co-administered to form a stable ternary complex of FdUMP, [6R]-5,10-methylenetetrahydrofolate (MTHF), and thymidylate synthase.[3] All folates currently approved for use in the mCRC clinical setting are prodrugs that need to be metabolically activated to [6R]-MTHF, the active thymidylate synthase cofactor that potentiates the effect of 5-FU **(Figure 1b)**.[4] In contrast, arfolitixorin consists of the active cofactor [6R]-MTHF and does not require multi-step metabolic activation.[4] Low expression of folate-activating genes may result in poor response to 5-FU/leucovorin due to insufficient levels of cofactor leading to weak inhibition of thymidylate synthase.[5,6] Excess [6R]-MTHF also favors competition at the thymidylate synthase binding site for FdUMP over deoxyuridine monophosphate (dUMP), potentially permitting more extensive and prolonged enzyme inhibition following 5-FU treatment **(Figure 1a)**.[4]

Pharmacokinetic evaluation of arfolitixorin in the Phase I/II study ISO-CC-002 showed that considerably higher intratumoral and intramucosal concentrations of [6R]-MTHF are achieved in patients receiving a single intravenous dose of arfolitixorin compared with levoleucovorin, at either of two equimolar dose levels.[7]

Preliminary data from the Phase I/II study ISO-CC-005, which evaluated the efficacy of arfolitixorin/5-FU, alone or in combination with irinotecan or oxaliplatin, with or without bevacizumab, reported early tumor shrinkage in 47% of first-line patients after 8 weeks. After up to 32 weeks of follow-up, preliminary best overall response rate (ORR) demonstrated greater than 30% reduction in tumor size from baseline in 58% of patients.[8] The most frequent adverse events were fatigue, nausea, neutropenia, diarrhea, vomiting, and neuropathy.[9]

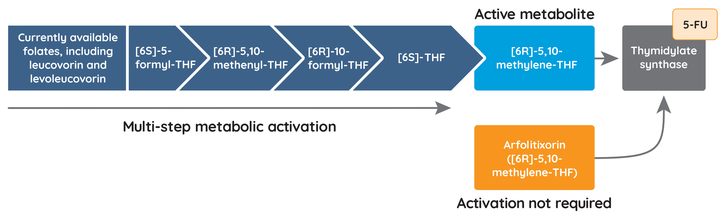
Evaluation of arfolitixorin in a larger randomized Phase III clinical setting is required to validate and extend these data.

Figure 1a. Mechanism of action of arfolitixorin



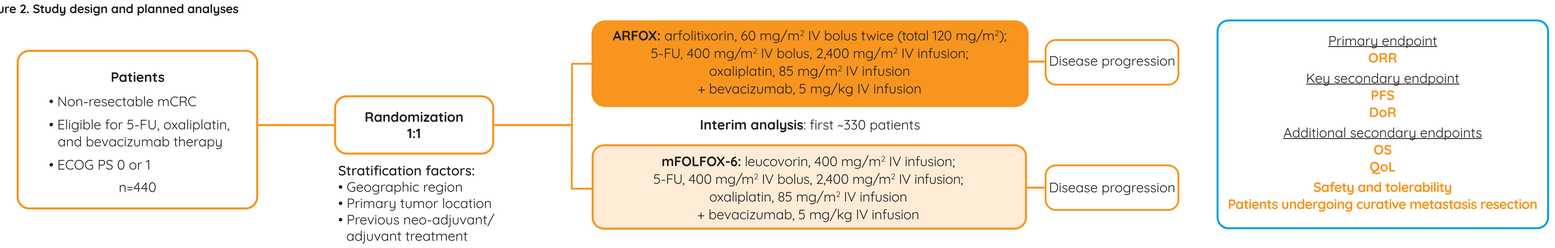
5-FU, 5-fluorouracil; MTHF, [6R]-5,10-methylenetetrahydrofolate; TS, thymidylate synthase

Figure 1b. Multi-step activation of folates



5-FU, 5-fluorouracil; THF, tetrahydrofolate

Figure 2. Study design and planned analyses



5-FU, 5-fluorouracil; ARFOX, arfolitixorin, 5-FU, and oxaliplatin; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; mCRC, metastatic colorectal cancer; mFOLFOX-6, modified FOLFOX-6 (leucovorin, 5-FU, and oxaliplatin); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life

STUDY RATIONALE

It is hypothesized that the administration of arfolitixorin will result in higher intracellular concentrations of the active thymidylate synthase cofactor [6R]-MTHF in all patients compared with leucovorin administration, with less inter- and intraindividual variability. In turn, this may translate to improved clinical efficacy in 5-FU treatment of mCRC.

STUDY DESIGN

This is a randomized, multicenter, parallel-group, Phase III study AGENT (NCT03750786) to compare the efficacy of arfolitixorin versus leucovorin in patients with mCRC treated with 5-FU, oxaliplatin, and bevacizumab.[10] Patients will be randomized in a 1:1 ratio to either the investigational arm (arfolitixorin + 5-FU + oxaliplatin [ARFOX] + bevacizumab) or the comparator arm (leucovorin + 5-FU + oxaliplatin [modified FOLFOX-6] + bevacizumab), and treated until occurrence of disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria **(Figure 2)**.

The study target is to randomize 440 patients in 18 months. An adaptive study design, intended to ensure sufficient statistical power while minimizing patient numbers, includes the possibility to increase the sample size to 660 patients, as determined by the Data and Safety Monitoring Board during the interim analysis to be carried out after 330 patients have undergone their 16-week scan **(Figure 2)**.

In addition, a translational program will evaluate the expression levels of several folate metabolism- and transportation-related genes in mCRC tumor biopsies in order to determine their relationship to treatment outcome. Genes to be analyzed include ATP-binding cassette C3 (ABCC3) transporter, methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), proton-coupled folate transporter (PCFT), and serine hydroxymethyltransferase 1 (SHMT1).

STUDY ENDPOINTS

The primary endpoint of the study will be ORR by blinded independent central review, defined as the best response from the start to the end of treatment **(Figure 2)**. Key secondary endpoints will include progression-free survival (PFS), defined as time from randomization to first occurrence of tumor progression based on computerized tomography (CT) scans/ magnetic resonance imaging (MRI), and duration of response (DoR), measured from when measurement criteria are first met for complete response/partial response until recurrent or progressive disease is first objectively documented. Additional secondary endpoints include overall survival (OS), quality of life (QoL), safety and tolerability, and patients undergoing curative metastasis resection.

KEY ELIGIBILITY CRITERIA

Key inclusion and exclusion criteria are listed in **Table 1**.

Table 1. Key eligibility criteria

Inclusion	Exclusion
Adults ≥18 years of age	Malignant tumors other than colorectal adenocarcinomas
Colorectal adenocarcinoma verified by biopsy	<6 months since last anti-cancer treatment
Availability of biopsy material, from the primary tumor or metastasis, allowing for analysis of tumor gene expression	Known dihydropyrimidine dehydrogenase deficiency
Non-resectable mCRC planned for first-line therapy with leucovorin, 5-FU, oxaliplatin, and bevacizumab	Clinically significant cardiovascular disease
Evaluable disease (via CT scan or MRI)	Central nervous system metastases
ECOG PS 0 or 1	
Adequate hematological function	
Adequate hepatic function	

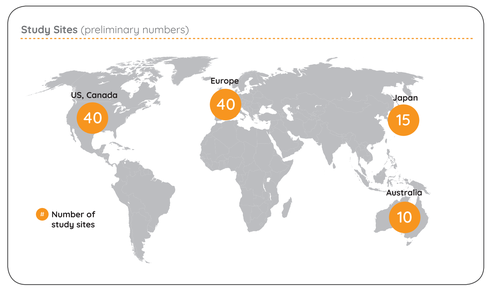
5-FU, 5-fluorouracil; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; PS, performance status

STUDY COUNTRIES

The AGENT study will take place across approximately 100 sites in the following countries **(Figure 3)**:

- Australia
- Austria
- Canada
- France
- Germany
- Greece
- Japan
- Spain
- Sweden
- USA

Figure 3. Sites participating in the AGENT study

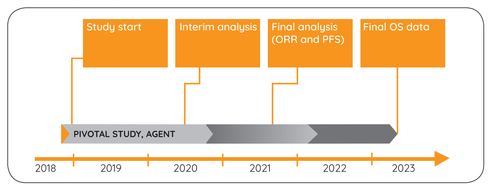


STUDY DATES

Key study milestones **(Figure 4)**:

- First patient in: December 18, 2018
- Interim analysis: mid 2020
- Final PFS data: Q3 2021
- Final OS data: TBD

Figure 4. Key study milestones



ORR, objective response rate; OS, overall survival; PFS, progression-free survival

SUMMARY

- In contrast to folates approved to treat mCRC, arfolitixorin does not require metabolic activation and may produce higher and less variable concentrations of [6R]-MTHF than the comparator leucovorin
- This Phase III study will compare the efficacy of first-line arfolitixorin vs leucovorin in combination with 5-FU, oxaliplatin, and bevacizumab in patients with mCRC
- Primary and key secondary endpoints will include ORR, PFS, and DoR
- Interim data are expected in mid 2020

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