An open-label Phase III study of arfolitixorin vs leucovorin in modified FOLFOX-6 for first-line treatment of metastatic colorectal cancer

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BACKGROUND

Current treatments and folate-based strategies

- First-line treatment of metastatic colorectal cancer (mCRC) is typically with cytotoxic chemotherapy, combined with biologics such as bevacizumab, cetuximab, or panitumumab[1]
- 5-fluorouracil (5-FU), co-administered with the folate leucovorin, is an established cornerstone of mCRC treatment.[1] 5-FU undergoes metabolic transformation to 5-fluorodeoxyuridine monophosphate (FdUMP), which potently inhibits the thymidylate synthase enzyme, in turn disrupting DNA synthesis and repair, and resulting in cell death in rapidly proliferating tumor cells **(Figure 1)**[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 clinical use in patients with mCRC are prodrugs that need to be metabolically activated to [6R]-MTHF, the active thymidylate synthase cofactor that potentiates the effect of 5-FU **(Figure 2)**[4]

Mechanism of action of arfolitixorin

- Arfolitixorin consists of the active cofactor [6R]-MTHF and therefore does not require multi-step metabolic activation[4]
- Response to 5-FU/leucovorin may be impaired by low expression of folate-activating genes due to insufficient levels of cofactor and, consequently, weak inhibition of thymidylate synthase[5,6]
- Excess [6R]-MTHF, however, 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 1)**[4]

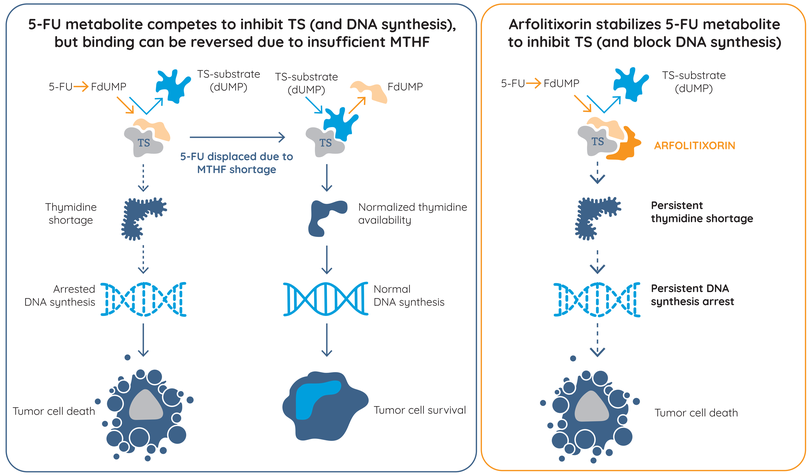
Arfolitixorin clinical data

- In the Phase I/II pharmacokinetics study ISO-CC-002, considerably higher intratumoral and intramucosal concentrations of [6R]-MTHF were achieved in patients receiving a single intravenous dose of arfolitixorin compared with levoleucovorin, at either of two equimolar dose levels, which is consistent with the potential for greater efficacy of arfolitixorin[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, and with or without bevacizumab, reported early tumor shrinkage in 47% of first-line patients after 8 weeks.[8] After up to 32 weeks of follow-up, preliminary overall response rate (ORR) was achieved in 58% of patients.[8] The most frequently reported adverse events were typical chemotherapy side effects, including fatigue, nausea, neutropenia, diarrhea, vomiting, and neuropathy[9]

Phase III evaluation of arfolitixorin

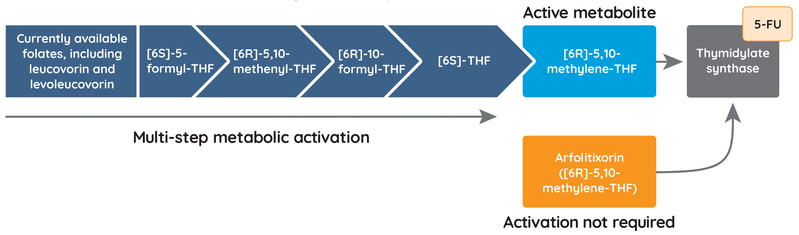
- Evaluation of arfolitixorin in a larger randomized Phase III clinical setting is required to validate and extend these data

Figure 1. Mechanism of action of arfolitixorin



5-FU, 5-fluorouracil; dUMP, deoxyuridine monophosphate; FdUMP, 5-fluorodeoxyuridine monophosphate; MTHF, [6R]-5,10-methylenetetrahydrofolate; TS, thymidylate synthase.

Figure 2. Multi-step activation of folates



5-FU, 5-fluorouracil; THF, tetrahydrofolate.

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 intra-individual 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 relative to that of 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 1.1 criteria **(Figure 3)** or unacceptable toxicity

KEY ELIGIBILITY CRITERIA

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

Table 1. Key eligibility criteria

Inclusion

- Adults ≥18 years of age
- Colorectal adenocarcinoma verified by biopsy
- Availability of biopsy material, from the primary tumor or metastasis, allowing for analysis of tumor gene expression
- Non-resectable mCRC planned for first-line therapy with leucovorin, 5-FU, oxaliplatin, and bevacizumab
- Evaluable disease (via CT scan or MRI)
- ECOG PS 0 or 1
- Adequate hematologic function
- Adequate hepatic function
- Adequate renal function

Exclusion

- Malignant tumors other than colorectal adenocarcinomas
- <6 months since last anti-cancer treatment
- Known dihydropyrimidine dehydrogenase deficiency
- Clinically significant cardiovascular disease
- Central nervous system metastases

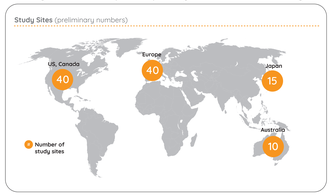
5-FU, 5-fluorouracil; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; PS, performance status.

STUDY COUNTRIES

The AGENT study will take place across more than 100 sites in the following countries **(Figure 4)**:

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

Figure 4. Sites participating in the AGENT study

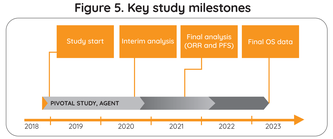


STUDY DATES

Key study milestones **(Figure 5)**:

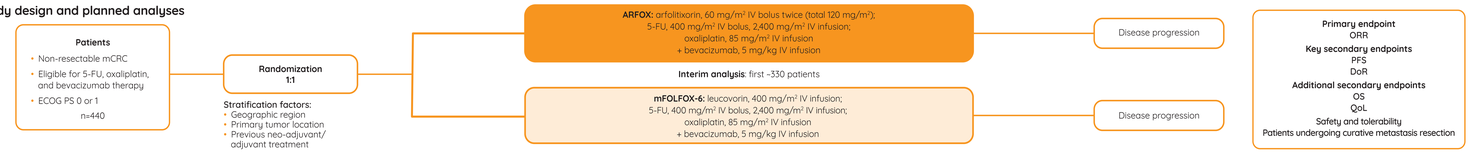
- First patient in: December 18, 2018
- Interim analysis: Q3 2020
- Final PFS data: Q3 2021
- Final OS data: TBD

Figure 5. Key study milestones



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

Figure 3. 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, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life.

PATIENTS

- Target recruitment includes randomization of 440 patients in 18 months and is currently ongoing **(Figure 4)**. 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 3)**

STUDY ENDPOINTS

- The primary study endpoint will be ORR by blinded independent central review, defined as the best response from the start to the end of study treatment **(Figure 3)**
- Key secondary endpoints will include progression-free survival (PFS), defined as time from randomization to first occurrence of tumor progression based on computerized tomography scans/magnetic resonance imaging or death, and duration of response (DoR), measured from when measurement criteria are first met for complete response/ partial response until progressive disease is first objectively documented
- Additional secondary endpoints include overall survival (OS), quality of life, safety and tolerability, and patients undergoing curative metastasis resection

EXPLORATORY ANALYSES

- A translational program will determine folate metabolism- and transportation-related gene expression levels in all patients
- Fixed-formalin paraffin-embedded mCRC tumor sections derived from biopsies obtained prior to treatment initiation will be used for gene expression analysis via a validated technique to be conducted at a central accredited laboratory in Gothenburg, Sweden
- Levels of the following genes will be retrospectively analyzed: adenosine triphosphate (ATP)-binding cassette C3 transporter, methylenetetrahydrofolate dehydrogenase 2, proton-coupled folate transporter, serine hydroxymethyltransferase 1, peptidylprolyl-isomerase A, and beta-actin

SUMMARY

- In contrast to folates currently approved to treat mCRC, arfolitixorin does not require metabolic activation and may produce higher and more consistent concentrations of [6R]-MTHF than the comparator leucovorin, which may in turn improve clinical efficacy
- This Phase III study will compare the efficacy of first-line arfolitixorin versus leucovorin in combination with 5-FU, oxaliplatin, and bevacizumab in patients with mCRC
- The primary endpoint will be ORR and key secondary endpoints will include PFS and DoR
- A translational program will explore the relationship between expression levels of key genes involved in folate metabolism and transport in mCRC tumor biopsies, and treatment efficacy
- Interim data are anticipated in Q3 2020 **(Figure 5)**

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