# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

10 Jun 2026

## A Phase III, randomized, two-armed, double-blind (patient and assessor blinded), parallel active controlled non-Inferiority clinical trial to evaluate the efficacy and safety of bevacizumab(AryoGen®) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC)

## Protocol summary

**Study aim**
The purpose of this study was to compare the efficacy and safety of the proposed bevacizumab biosimilar to the reference product in patients with metastatic colorectal cancer mCRC

**Design**
This phase III, randomized, two-armed, parallel, double-blinded (patient- and assessor-blinded), active-controlled, multicenter, noninferiority study was conducted in 22 centers across nine cities of Iran. The randomization plan of the 126 patients will be carried out using an on-line system (http://www.randomization.com).

**Settings and conduct**
This phase III, randomized, two-armed, parallel, double-blinded (patient- and assessor-blinded), active-controlled, multicenter, noninferiority study was conducted in 22 centers across nine cities of Iran

**Participants/Inclusion and exclusion criteria**
According to criteria

**Intervention groups**
Study Drug(Arm A): FOLFIRI3 , Bevacizumab (AryoGen Pharmed) Control (Arm B): FOLFIRI3 , Bevacizumab (Avastin)

**Main outcome variables**
The primary endpoint was progression-free survival (PFS), which was defined as the time from the date of randomization to the first date of documented progression or death as a result of any cause.1 year after randomization

## General information

**Reason for update**
Updating the inclusion and exclusion data, updating of centers, editing of primary and secondary outcome

**Acronym**

**IRCT registration information**
IRCT registration number: **IRCT2015072517994N2**
Registration date: **2016-07-28, 1395/05/07**
Registration timing: **prospective**

Last update: **2020-11-19, 1399/08/29**
Update count: **1**

**Registration date**
2016-07-28, 1395/05/07

**Registrant information**

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**Recruitment status**
**Recruitment complete**

**Funding source**
AryoGen Pharmed Company

**Expected recruitment start date**
2016-08-22, 1395/06/01

**Expected recruitment end date**
2016-08-22, 1395/06/01

**Actual recruitment start date**
2016-10-04, 1395/07/13

**Actual recruitment end date**
2017-07-30, 1396/05/08
**Trial completion date**
2018-07-30, 1397/05/08

**Scientific title**
A Phase III, randomized, two-armed, double-blind (patient and assessor blinded), parallel active controlled non-Inferiority clinical trial to evaluate the efficacy and safety of bevacizumab(AryoGen®) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC)

**Public title**
Evaluation the efficacy and safety of bevacizumab in comparison with bevacizumab (Avastin®) as a first line therapy in patients with metastatic colorectal cancer (mCRC)
**Purpose**
Treatment
**Inclusion/Exclusion criteria**
**Inclusion criteria:**
Inclusion criteria: Male or female aged 18-75 years at the time of signing the informed consent form, have been diagnosed as mCRC verified histologically, having one or more bi-dimensionally measurable lesions as defined by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, was not felt to be amenable to curative resection, with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, life expectancy of longer than 3 months ( clinical assessment), adequate organ and marrow function as defined below: Absolute neutrophil count (ANC) greater than/equal to 1,500/mm3; o Platelets greater than/equal to 100,000/ mm3; o Hemoglobin greater than/equal to 9 gm/dl (may be transfused to maintain or exceed this level); o Total bilirubin less than/equal to 1.5 within institutional upper limit of normal (IULN); Aspartate aminotransferase (AST or SGOT)/alanine aminotransferase (ALT or SGPT) less than/equal to 2.5 times IULN, or less than/equal to 5 times IULN if known liver metastases, may have received adjuvant therapy for primary colorectal cancer provided that at least 6 months have elapsed from the time the adjuvant therapy was concluded and recurrent disease was documented, Patients with history of hypertension must be well-controlled (blood pressure less than/equal to 150/100mmHg), on a stable regimen of anti-hypertensive therapy.
**Exclusion criteria:**
Exclusion criteria, Radiotherapy or surgery for mCRC less than 4 weeks before random assignment, Undergone major surgical procedures or open biopsy within 28 days before the initiation of study treatment, experienced a significant traumatic injury, within 28 days before study entry, currently using or had recently used therapeutic anticoagulants, thrombolytic therapy, chronic, daily treatment with aspirin( higher than 325 mg/daily). (Patients may have prophylactic use of low molecular weight heparin, however therapeutic use of heparin or low molecular weight heparin is not acceptable) - Proteinuria exceeding 500mg/24h - History or presence of central nervous system metastases - Female patients who are pregnant or lactating - Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab, irinotecan, 5-FU, or leucovorin - Serious non-healing wound, ulcer, or an active bone fracture - Patients with any history of another primary malignancy less than/equal to 5 years, with the exception of non-melanoma skin cancer, and carcinoma in situ of the uterine cervix. - Myocardial infarction within 6 months before of study enrollment; - History of stroke within 6 months before of study enrollment; - Unstable symptomatic arrhythmia requiring medication; - Clinically significant peripheral vascular disease; - Uncontrolled diabetes; Serious active or uncontrolled infection - Inability to comply with study and/or follow-up procedures
**Age**
From **18 years** old to **75 years** old
**Gender**
Both

**Phase**
3
**Groups that have been masked**
*No information*
**Sample size**
Target sample size: **126**
Actual sample size reached: **126**
**Randomization (investigator's opinion)**
Randomized
**Randomization description**
The randomization plan of the patients will be carried out using an on-line system (http://www.randomization.com). Using permuted block randomization (length of each block is 6) will be made, for a total of 126 patients (with 2:1 allocation ratio). Once the randomization has been made, each patient is given a code with which he will be identified throughout the study. The assigned code will be denoted by 4 initials (corresponding to the 2 first letter of the first name, the 2 first letter of the first surname), and 3 numbers (center code). Moreover, the code described is followed by study unique identification consisting of the first two letters of the generic name and study phase, respectively (which is BE3-) and 4 numbers (corresponding to the randomization number), e.g. ABCD001BE3-0001. The randomization number will be assigned in a consecutive way.
**Blinding (investigator's opinion)**
Double blinded
**Blinding description**
Each study's drug package for the course of a patient's treatment had a 3-digit number similar to the randomization code, so as long as the random code was unique, each patient had a unique drug package that will be completely identified with the randomized process.
**Placebo**
Not used
**Assignment**
Parallel
**Other design features**

## Secondary Ids

### 1

**Registry name**
ClinicalTrials.gov
**Secondary trial Id**
NCT03288987
**Registration date**
2018-07-30, 1397/05/08

## Ethics committees

### 1

**Ethics committee**
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**Approval date**
2016-06-21, 1395/04/01
**Ethics committee reference number**
IR.SBMU.REC.1395.4

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**Approval date**
2016-08-24, 1395/06/03
**Ethics committee reference number**
IR.AJUMS.REC.1395.351

## Health conditions studied

### 1

**Description of health condition studied**
Metastatic colorectal cancer
**ICD-10 code**
C18-9
**ICD-10 code description**
Malignant neoplasm of colon

## Primary outcomes

### 1

**Description**
progression-free survival
**Timepoint**
1 year after randomization
**Method of measurement**
Method of measurement: the time from the date of randomization to the first date of documentation progression (per investigator assessment) or death as a result of any cause.

## Secondary outcomes

### 1

**Description**
Overall survival: the time from date of randomization to date of death due to any cause.Overall response rate: partial and complete responses, according to the RECIST criteria.Time to treatment failure: as the time from the date of randomization to the date of each of the following: The treatment modalities did not destroy or modify the cancer cell, the tumor either became larger (disease progression) or stayed the same size after treatment, Death from any cause, Discontinuation of treatment.Safety: Safety will be assessed based on adverse events reports, the results of laboratory tests, vital signs and immunogenicity. All adverse events are categorized by CTCAE (v. 5.0) guideline of the American National Cancer Institute.
**Timepoint**
During one year after randomization
**Method of measurement**
time based on month, RESICT guidline

## Intervention groups

### 1

**Description**
Intervention (Arm A): FOLFIRI - 3+bevacizumab(AryoGen®) FOLFIRI - 3: In this group FOLFIRI-3 regimen consists of irinotecan 100 mg/m2 over 1 hour at day 1, leucovorin 400 mg/m2 at day 1 followed by a 46 hour 5-FU continuous infusion (2400 mg/m2), and irinotecan 100 mg/m2 over 1 hour at day 3 will administer. Drug: Bevacizumab ( AryoGen ®) 5 mg/kg will administer every 2 weeks. Initially, it will administer as a 90 min infusion. If the first infusion is well-tolerated, the second will deliver as a 60 min infusion; if the 60-min infusion is well tolerated; all subsequent infusions will deliver over 30 min
**Category**
Treatment - Drugs

### 2

**Description**
Active Comparator(Arm B) FOLFIRI - 3 + Bevacizumab

(Avastin) FOLFIRI-3: In this group FOLFIRI-3 regimen consist of irinotecan 100 mg/m2 over 1 hour at day 1, leucovorin 400 mg/m2 at day 1 followed by a 46 hour 5-FU continuous infusion (2400 mg/m2), and irinotecan 100 mg/m2 over 1 hour at day 3 will administer. Drug: Bevacizumab (Avastin) 5 mg/kg will administer every 2 weeks. Initially it will administer as a 90 min infusion. If the first infusion is well tolerated, the second will deliver as a 60 min infusion; if the 60-min infusion is well tolerated; all subsequent infusions will deliver over 30 min

**Category**

Treatment - Drugs

## Recruitment centers

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**Grant name**
**Grant code / Reference number**
**Is the source of funding the same sponsor organization/entity?**
Yes
**Title of funding source**
Aryogene pharmed company
**Proportion provided by this source**
100
**Public or private sector**
Private
**Domestic or foreign origin**
Domestic
**Category of foreign source of funding**
*empty*
**Country of origin**
**Type of organization providing the funding**
Industry

## Person responsible for general inquiries

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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**

Undecided - It is not yet known if there will be a plan to make this available

**Study Protocol**

Undecided - It is not yet known if there will be a plan to make this available

**Statistical Analysis Plan**

Undecided - It is not yet known if there will be a plan to make this available

**Informed Consent Form**

Undecided - It is not yet known if there will be a plan to make this available

**Clinical Study Report**

Undecided - It is not yet known if there will be a plan to make this available

**Analytic Code**

Undecided - It is not yet known if there will be a plan to make this available

**Data Dictionary**

Undecided - It is not yet known if there will be a plan to make this available