Study Protocol

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 Pharmed) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC).

Version: 6.4

Date: 3 April 2017

Contents

Confidential Information

The confidential information in the following document is provided to you as an investigator, auditor, and sponsor for review by you, your staff and an ethics committee and food and drug administration. By accepting this document, you agree that the information contained herein will not be disclosed to others without written authorization from AryoGen Pharmed Co., except to the extent necessary to obtain informed consent from those persons to whom the products may be administered. By signing below, the investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by AryoGen Pharmed Co., prior to seeking approval from the Independent Ethics Committee (IEC).

This study will be conducted in accordance with Good Clinical Practices (GCPs), the Declaration of Helsinki, local, ethical, and legal requirements.

Chief Investigator: Dr. Hamid Rezvani

Affiliation: Hematology and oncology Center, Taleghani Hospital, Shahid Beheshti university of medical sciences, Tehran, Iran.

Signature:

Date: ……/……. /……

Sponsor representative: Dr. Araz Sabzvari

Signature:

Date: ……/……. /… ……

Contract Research Organization representative: Dr. Hamed Hosseini

Signature:

Date: ……/……. /……

Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
CEA	Carcinoembryonic Antigen
CRC	Colorectal Cancer
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiography
EGFR	Epidermal growth-factor receptor
FAP	Familial Adenomatous Polyposis
FOLFIRI	5-fluorouracil, leucovorin and irinotecan
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
HCT	Hematocrit
Hgb	Hemoglobin
HNPCC	Hereditary nonpolyposis colorectal cancer
IBD	Inflammatory Bowel Disease
ICD	Informed Consent Document
ICF	Informed Consent Form
IFDA	Iran Food and Drug Administration
IRCT	Iranian Registry of Clinical Trial
LDH	Lactate Dehydrogenases

LFT	Liver Function Test
mCRC	Metastatic Colorectal Cancer
OS	Overall Survival
PFS	Progression Free Survival
PI	Principle Investigator
RFT	Renal Function Test
VEGF	Vascular Endothelial Growth Factor

Administrative information

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 pharmed) plus FOLFIRI-3 in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 as a first line therapy in patients with metastatic colorectal cancer (mCRC).

Trial registration

It is planned to register this protocol to Iranian Registry of Clinical Trial (IRCT) http://IRCT.ir

Registration code in IRCT: IRCT2015072517994N2

Ethics committee code has been received in 1395/05/02 from Shahid Beheshti university of medical sciences with the number of IR.SBMU.REC.1395.4. with letter number of 1395/ص/25912.

Ethics committee code has been received in 1395/06/03 from Ahwaz Jondi-Shapur university of medical sciences with the number of IR.AJUMS.REC.1395.351. with letter number of 3787/د/8/20/پ

Clinical Trial Authorization (CTA) from food and drug administration of Iran with the number of 665/111592 in 1395/07/13.

Protocol version

Version: 6.4 Date: 96.01.14

Funding

Bevacizumab (AryoGen pharmed) will be manufactured by AryoGen pharmed and bevacizumab (Avastin®) will be provided by AryoGen pharmed. All trial costs will be provided by Aryogen pharmed.

Roles and Responsibilities

Sponsor

AryoGen pharmed Company

Contact address: AryoGen pharmed, No. 140, Corner of Tajbakhsh St., 24th Km Tehran-Karaj Makhsous Road, Alborz, Iran

Tel: +98 26 36106480-4

Fax: +98 26 36104644

Zip Code: 3164819711

Sponsor representative: Dr. Araz Sabzvari

Contact address: Orchid Pharmed Company, No 42, Attar St, Tehran, Iran.

Telephone: 00982143473600

Role:

- Preparing final draft of study protocol
- Obtaining necessary approvals from external organizations for the conduct of study
- Providing standard operational procedures (SOP) for principle investigators in participating centers
- Providing quality controlled drugs to be used in the trial and delivery to participating centers
- Funding provision for all activities foreseen in study protocol via signing contracts with principal investigator
- Providing compensation for patients who may be adversely affected by participating in the trial
- Providing insurance coverage for all study participants
- Providing necessary training for staff
- Recruiting necessary workforce to conduct monitoring of the trial
- All expenses will be the responsibility of the sponsor.

- Audit of study sites to review the process of conducting the study and report the cases of violations from the protocol.

Representatives of the sponsor to conduct an audit to monitor the quality of the study:

Name: Dr. Nasim Anjidani, Pharmacist, Medical Manager

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Name: Mr. Siavash Bakhshian, Clinical Trial Manager

Contact address: Orchid Pharmed Company, No 42, Attar St, Tehran, Iran.

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Name: Mrs. Elham Farhangara, Clinical Trial Coordinator

Contact address: Orchid Pharmed Company, No 42, Attar St, Tehran, Iran.

Telephone: 00982143473162 Email: Farhangara.e@orchidpharmed.com

Roles:

- Visiting study sites to review the process of the protocol and ensure that the study is conducted in accordance with the protocol and GCP principles (at least one or two of these persons will attend each visit).
- Check the site's facilities for the performance and continuation of the clinical trials and take the necessary measures to provide them (to ensure that enough drugs are available to continue the study, to ensure that enough CRF and consent forms are met, and other requirements for the performance of the study).
- Persistent training of site personnel for protocol performance.
- Checking CRFs and matching them with source data and filling out the query for noncompliance and reminding them to correct them.

- Provide reports of non-compliances and facilities required by the site and submit it to the company's managers.

Representative of the sponsor for external monitoring on quality control of the study:

Name: CRO Trial

Name: Dr. Hamed Hosseini, Tehran University of medical sciences

Contact address: Tehran University of medical sciences, Institute of Research and Research Centers, Keshavarz Blvd., North Kargar St., Tehran, Iran.

Telephone: 00982188963546

Signature:

Name: Dr. Mansour Shamsipour, Tehran university of medical sciences

Contact address: Tehran university of medical sciences, Institute of Research and Research Centers, Keshavarz Blvd., North Kargar St., Tehran, Iran.

Telephone: 00982188963546

Signature:

Roles:

- Preparing a randomization file
- Conducting a 70% monitoring in all of the sites participating in the study according to GCP Guidelines, 126 patients were diagnosed in patient recruitment centers.
- Supervision over the study and Data Management
- Performing Statistical analysis and Preparing or approving the project either in middle or the end of the study
- Cooperation with company to perform Monitoring visits
- Cooperation for answering the methodology queries
- Regular visiting of all patient sites of Tehran

Chief investigator:

Name: Dr. Hamid Rezvani, Professor of Hematology and Oncology

Role:

- ✓ Conducting the study according to the agreed protocol
- ✓ Setting up a team for this purpose
- ✓ All clinical examinations
- ✓ Responsible for conducting trial according to ICH-GCP in sites.
- ✓ Organizing training events for their existing and newly recruited team members wherever necessary
- ✓ Provision of suitable storage and delivery for drugs used in the trial
- ✓ Cooperation with monitors during the conduct of the study
- ✓ No part of this trial could be published without the prior agreement with sponsor. (This agreement must be signed by PI and sponsor before the study initiation.)
- ✓ Responsible to provide training for staff at the study site
- ✓ Patients care
- ✓ Notification of AEs and ADRs to sponsor and regulatory according to the protocol schedule and regulatory requirements.

Contact address: Hematology and oncology Center, Fourth floor, Taleghani Hospital, Shahid Beheshti university of medical sciences, Tehran, Iran.

Signature:

Principal investigators

Roles:

- Conducting the study according to the agreed protocol
- Setting up a team for this purpose
- Organizing training events for their existing and newly recruited team members whenever necessary
- Provision of suitable venues for patient's admission
- Provision of suitable storage for drugs used in the trial

- Cooperation with monitors during the conduct of the study
- All medical documents related to the trial should be sent to AryoGen pharmed Company at the end of the trial. A copy may be kept by principle investigator
- No part of this trial could be published without the prior agreement of AryoGen Pharmed Company.

In all of these centers, patient recruitment is performed.

Researcher name and address:

- **Taleghani Hospital**

  Contact address: Hematology and oncology center, Fourth floor, Shahid Beheshti university of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran.

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  - Dr. Mojtaba Ghadyani, Shahid Beheshti university of medical sciences
  - Dr. Sina Salari, Shahid Beheshti university of medical sciences

- **Emam Khomeini Hospital**

  Contact address: Hematology and oncology center, Valiasr hospital, Imam Khomeini Therapeutic Complex, Keshavarz blvd., Tehran, Iran.

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  - Dr. Farhad Shahi, Tehran university of medical sciences

- **Shariati Hospital**

  Contact address: East Jalal al Ahmad highway, Tehran, Iran.

  Telephone: 00982184901000

  - Dr. Davood Babakhani, Tehran university of medical sciences.
  - Dr. Mohammad Vaezi, Tehran university of medical sciences.

- **Sina Hospital**

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  - Dr. Mohsen Esfandbod, Tehran university of medical sciences.

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  - Dr. Adnan Khosravi, Shahid Beheshti university of medical sciences.

- **Firoozgar Hospital**

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  Telephone: 00982182141600

  - Dr. Mohsen Razavi, Iran university of medical sciences.

- **Artesh 501 Hospital**

  Contact address: Shahid Etemad Zadeh St. West Fatemi St., Tehran, Iran.

  Telephone: 00982186096350

  - Dr. Mohsen Rajaei Nejad, Artesh university of medical sciences.

- **Masoud Clinic**

  Contact address: No. 144., 19th St., after Jalal Al Ahmad Highway, North Kargar St., Tehran, Iran.

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  - Dr. Masoud Iravani, Tehran university of medical sciences.

- **Dr. Safa Najar Najafi Clinic**

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  - Dr. Safa Najar Najafi, Tehran university of medical sciences.

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  - Dr. Valiollah Mehrzad, Isfahan university of medical sciences

  - Dr. Amir Abas Nekoyi, Isfahan university of medical sciences

  - Dr. Ali Haji Gholami, Isfahan university of medical sciences

  - Dr. Alireza Sadeghi, Isfahan university of medical sciences

- **Saba Clinic**

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  - Dr. Mohsen Khani, Isfahan university of medical sciences.

- **Mashhad Emam Reza Hospital**

  Contact address: Emam Reza square, Ebne Sina St., Mashhad, Khorasan Razavi.

  Telephone: 00985138543031

  - Dr. Abolghasem Allahyari, Mashhad university of medical sciences.

- **Mashhad Ghaem Hospital**

  Contact address: Emam Reza square, Ebne Sina St., Mashhad, Khorasan Razavi, Iran.

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  - Dr. Rahimi, Mashhad university of medical sciences.

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  - Dr. Babak Shazad, Kermanshah university of medical sciences.

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  - Dr. Mohammad Reza Mortazavi Zadeh, Yazd university of medical sciences.
  - Dr. Mohammad Reza Vahidfar, Yazd university of medical sciences

- **Dr. Mohammadreza Mortazavi Zadeh Clinic**
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  Telephone: 00983537250044
  - Dr. Mohammadreza Mortazavi Zadeh, Yazd university of medical sciences.

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  - Dr. Mani Ramzi, Shiraz university of medical sciences.
  - Dr. Alireza Rezvani, Shiraz university of medical sciences.

- **Ahwaz Shafa Hospital**
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  - Dr. Mohammad Segholeslami, Ahwaz university of medical sciences.
  - Dr. Ahmad Ahmad Zadeh Deilami, Ahwaz university of medical sciences.

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- Dr. Sirus Gharib, Rasht university of medical sciences.

- **Rasht Rasoul Hospital**

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  Telephone: 00981333665652

  - Dr. Mehdi Mirbolouk, Rasht university of medical sciences.

- **Hamedan Shahid Beheshti Hospital**

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  - Dr. Mohammad Abasi, Hamedan university of medical sciences.

Statistical adviser

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- **Name**: Ameneh Valujerdi

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- **Name**: Dr. Ali Akhlaghi

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Role: evaluating and analysis of trial data

Scientific steering committee

- Name: Dr. Hamid Rezvani, Oncologist, Shahid Beheshti University of medical sciences.

Contact address: Oncology and hematology center, Fourth floor, Taleghani hospital, Shahid Beheshti University of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran.

Telephone: 00982122937031

- Name: Dr. Sina Salari, Oncologist, Shahid Beheshti university of medical sciences.

Contact address: Oncology and hematology center, Fourth floor, Taleghani hospital, Shahid Beheshti University of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran.

Telephone: 00982122937031

Roles:

1- Establishing coordination among researchers in study centers.
2- Monitor and review the reports provided by the sponsor and CRO.
3- Signing of the protocol and protocol amendments and reports submitted to the Food and Drug Administration of Iran and ethics committees on behalf of other professors.
4- Adopting a proper decision to address the conditions in which the profit-risk balance for participants in the study, either individually or in general, conflicts. With regard to safety information, these decisions may include the identification of the relationship between the drug and the unwanted event observed, the adoption of appropriate strategies for the continuation of study and the departure of the person who is no longer eligible for the study.
5- Make the right decision to decode the drug.
6- Investigator meeting at least once a month (every two weeks, the report of study and patient's status is fully described to Dr. Rezvani and his consultant, Dr. Salari.).

Introduction

Background and rationale

Epidemiology

Colorectal carcinoma is a common malignancy and a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidences. It is the third most common cancer worldwide and the fourth most common, cause of death (The third most commonly diagnosed cancer in males and the second in females). [(1)]. CRC is the third leading cause of cancer worldwide and accounts for 10% of all new cancer diagnoses. 20% of patients will have metastatic disease at presentation and a further 30% of those diagnosed with early stage CRC will develop metastatic disease. [(4)]. Colorectal cancer survival is highly dependent upon stage of disease at diagnosis, and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage; 70% for regional; to 10% for people diagnosed for distant metastatic cancer. In general, the earlier the stage at diagnosis associated with the higher the chance of survival. Survival is extremely limited in stage IV colon carcinoma. The most common site of metastasis is the liver. The second most common site of metastasis is the lung, occurring in approximately 20% of patients with colorectal carcinoma. The patients with stage IV disease (mCRC) cannot be cured surgically; newer chemotherapeutic regimens have significantly improved response and tumor shrinkage. [(1, 2, 3)]

Etiology

Approximately 5 to 10% of colorectal cancers are a consequence of recognized hereditary conditions. The most common inherited conditions are familial adenomatous polyposis (FAP) and hereditary non-polyposis, colorectal cancer (HNPCC), also called Lynch syndrome. Genes responsible for these forms of inherited colorectal cancer have been identified. HNPCC is associated with mutations in genes in the DNA repair pathway, namely the MLH1 and MSH2 genes, which are the responsible mutations in individuals with HNPCC. FAP is caused by mutations in the tumor suppressor gene APC. [(5)]

Treatment

Current standard of care first-line treatments for mCRC include FOLFOX and FOLFIRI. Since 2004, targeted therapies alone or in combination with standard chemotherapies have provided more treatment options and better results. These include the VEGF monoclonal antibody and

the EGFR monoclonal antibodies. Today the standard treatment of mCRC in the first-line setting combines chemotherapy regimens with antibody therapy. As chemotherapy backbones infusional 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine with either irinotecan (FOLFIRI/CAPIRI) or oxaliplatin (FOLFOX/CAPOX) are administered. Additionally, the monoclonal antibodies cetuximab and bevacizumab have shown activity and were approved in combination with FOLFOX/CAPOX and/or FOLFIRI/CAPIRI for first-line chemotherapy in mCRC. [6, 7]

The first drug of choice for patients with mCRC was the fluoropyrimidine 5- fluorouracil (5-FU). Bolus FU led to modest response rates of approximately 12% and a median survival of approximately 11 months. Combining FU with leucovorin (LV) improves clinical outcomes. Researches have showed that irinotecan or oxaliplatin plus FU/LV known as IFL and FOLFOX, respectively, significantly improve outcomes. [8] In the other hand, in the study performed by Bidard et al, FOLFIRI3 has shown promising results in second-line PFS vs. FOLFIRI and other various irinotecan-based regimens for mCRC patients previously exposed to oxaliplatin [9]. Another study by Kim et al, has shown, FOLFIRI-3-bevacizumab is associated with an acceptable toxicity and induced promising objective response. [10]

Bevacizumab

Angiogenesis is critical to both the growth of the primary tumor and metastases. Poor prognosis and an increased relapse rate are often correlated with increased blood vessel density in the primary tumor in mCRC. One of the most important stimulators of angiogenesis is VEGF. The potential of VEGF as an anticancer target was supported by the demonstration that a murine anti-VEGF monoclonal antibody can inhibit the growth of human tumor xenografts Subsequently, a recombinant humanized monoclonal antibody against VEGF, Bevacizumab (Avastin®), has been examined as an antiangiogenic cancer therapy. [11]

In addition to its direct antiangiogenic effects, bevacizumab may also improve the delivery of chemotherapy by altering tumor vasculature and decreasing the elevated interstitial pressure in tumors.

In mCRC patients, initial studies of Bevacizumab showed improvements in tumor response rate and progression-free survival (PFS) when added to fluorouracil and leucovorin. Subsequent randomized trials showed Bevacizumab to prolong median overall survival (OS;

20.3 versus 15.6 months) in combination with FOLFOX and to improve response rates and PFS times with the addition of Bevacizumab to FOLFIRI or FOLFOX in patients with untreated MCRC. [11, 12]

The pivotal trial of bevacizumab in mCRC patients demonstrated the benefit of adding the agent to irinotecan with bolus 5-FU and LV (IFL) in first-line treatment. Given the similar efficacy profiles of these latter two regimens, along with evidence for the superiority of FOLFIRI–bevacizumab over modified IFL–bevacizumab, it was assumed that FOLFOX and FOLFIRI could be used interchangeably with bevacizumab as first-line treatment. [13] Treatment with bevacizumab in combination with FOLFIRI for the first-line regimen resulted in an overall response rate of 53.1%. In terms of survival, patients treated with bevacizumab plus FOLFIRI had a median PFS of 11.1 months. Addition of bevacizumab to each of the chemotherapy regimens resulted in improved PFS of 11.2 months in the FOLFIRI arm (vs. 7.6 months for FOLFIRI alone) and 8.3 months in the mIFL arm (vs. 5.9 months for mIFL alone). Further support for the use of bevacizumab in combination with FOLFIRI comes from a single-arm phase II trial in which 43 patients had a median PFS of 12.5 months and 1-year survival rate of 95%. Two observational studies, BRiTE and BEAT, were designed to evaluate the safety and efficacy of bevacizumab in large, less-selected, community-based patient populations. Patients treated with bevacizumab plus FOLFIRI achieved a median PFS of 10.9 months (95% CI: 9.7–11.8) in the BRiTE study and 11.6 months in the BEAT study. In the BEAT study, the median OS for patients receiving bevacizumab plus FOLFIRI was 23.7 months compared with 22.7 months for the total patient population. Antiangiogenic therapy with bevacizumab plus FOLFIRI is an effective and well-tolerated regimen for the first-line treatment of metastatic CRC, and appears to be equally effective in clinical trials and community-based settings. Available data suggest that bevacizumab, combined with FOLFIRI or any fluoropyrimidine- containing chemotherapy regimen, should be considered as the therapy of choice for the treatment of patients with metastatic CRC. [14]

Bevacizumab common adverse events:

Lethargy, weakness, mild fever, chills, mild headache, rhinitis, tinnitus, sore throats, paresthesia, gingivitis, swelling or ulcers in the lips and mouth, nausea, vomiting and decreased appetite, skin reactions (including erythrodysesthesia, rash), tachycardia and bradycardia, restlessness, chest pain and dyspnea, decreased urine volume, painful urination, dark stools, venous thromboembolic complications, hypertension, bleeding events, Gastrointestinal

perforation, arterial thromboembolism complications, wound healing problems, fistula or abdominal abscess, proteinuria.

Rationale:

Bevacizumab is effective in various types of cancer and already this drug is used in treatment of patients of metastatic colorectal cancer, non-small cell carcinoma. This drug (Avastin®) was produced by Genentech Company a member of the Roche Groups in the USA. Because Bevacizumab is so expensive, production of this drug in our country with the same quality is very important. So, the purpose of this study is comparing the efficacy and safety characteristics of bevacizumab (AryoGen pharmed ®) in comparison with bevacizumab (Avastin®) to irinotecan plus leucovorin/continuous 5-fluorouracil [FOLFIRI -3] in patients with metastatic colorectal cancer (mCRC).

Objectives

The evaluation of non-inferiority of efficacy and safety of bevacizumab (AryoGen pharmed) in comparison with bevacizumab (Avastin®) plus FOLFIRI-3 (irinotecan plus leucovorin/5-fluorouracil as continuous infusion) and immunogenicity assay in patients with metastatic colorectal cancer (mCRC).

Primary objective(s)

To determine the non-inferiority of the efficacy of bevacizumab (AryoGen pharmed) versus bevacizumab (Avastin®) in progression free survival (PFS) when added to FOLFIRI- 3 (irinotecan plus leucovorin/ 5-fluorouracil as continuous infusion) in patients with metastatic colorectal cancer (mCRC).

Secondary objective(s)

The secondary purposes of this study are to establish the overall survival, tumor response rate, time to treatment failure (TTF) and to assess the safety and immunogenicity in bevacizumab (AryoGen pharmed) group in comparison with bevacizumab (Avastin®) group.

Trial Design

This is a, Phase III, randomized, two arms, double blind (patient and assessor blinded), parallel active non-inferiority controlled clinical trial with a 2:1 allocation.

Methods

Study setting

This trial will be initiated from October 2016 and 126 patients with metastatic colorectal cancer will be recruited from below centers. All centers implement same protocol and procedures. Procedures will standardize as completely as possible and variation of evaluation criteria and schemes will be reduced by investigator meetings, training of personnel in advance of the trial, and by careful monitoring during the trial.

1- Taleghani Hospital

Contact address: Hematology and oncology center, Fourth floor, Shahid Beheshti university of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran.

2- Emam Khomeini Hospital

Contact address: Hematology and oncology center, Valiasr hospital, Imam Khomeini

3- Shariati Hospital

Contact address: East Jalal al Ahmad highway, Tehran, Iran.

4- Sina Hospital

Contact address: Hasan Abad Square, Emam Khomeini St., Tehran, Iran.

5- Masih Daneshvari Hospital

Contact address: Hematology and Oncology center, Darabad St., Shahid Bahonar

6- Firoozgar Hospital

Contact address: Beh Afarin St. Karim khan Zand St. Valiasr square, Tehran, Iran.

7- Artesh 501 Hospital

Contact address: Shahid Etemad Zadeh St. West Fatemi St., Tehran, Iran.

8- Masoud Clinic

Contact address: No. 144., 19th St., after Jalal Al Ahmad Highway, North Kargar St., Tehran, Iran.

9- Dr. Safa Najar Najafi Clinic

Contact address: No. 15., Pardis St. Molla sadra St., Tehran, Iran.

10- Isfahan Sheikh Mofid Clinic

Contact address: Sheikh Mofid St., Feiz St., Isfahan, Iran.

11- Saba Clinic

Contact address: Saba Building, Mohammad Abad alley, Opposite Venus hotel, Amadgah St., Isfahan, Iran.

12- Mashhad Emam Reza Hospital

Contact address: Emam Reza square, Ebne Sina St., Mashhad, Khorasan Razavi.

13- Mashhad Ghaem Hospital

Contact address: Emam Reza square, Ebne Sina St., Mashhad, Khorasan Razavi, Iran.

14- Dr. Mehrdad Payandeh Clinic

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15- Dr. Babak Shazad Clinic

Contact address: Third floor, Mahdieh Building, Javanshir St., Kermanshah, Iran.

16- Yazd Seyedshohada Hospital

Contact address: Emam Khomeini St., Yazd, Iran.

17- Dr. Mohammadreza Mortazavi Zadeh Clinic

Contact address: No 25, Shahid haj Mohammadi Alley, Yazd, Iran.

18- Shiraz Namazi Hospital

Contact address: Namazi square, Zand St., Shiraz, Fars, Iran.

19- Ahwaz Shafa Hospital

Contact address: Golestan St., Ahwaz, Khoozestan, Iran.

20- Rasht Razi Hospital

Contact address: Sardar Jangal St., Rasht, Guilan, Iran.

21- Rasht Rasoul Hospital

Contact address: Guil square., Rasht, Iran.

22- Hamedan Shahid Beheshti Hospital

Contact address: Eram BLVD., Ghaem square, Hamedan, Iran.

Eligibility criteria

Inclusion criteria

This study will include participants who:

- Are 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/mm^3;
    - Platelets greater than/equal to 100,000/ mm^3;
    - Hemoglobin greater than/equal to 9 gm/dl (may be transfused to maintain or exceed this level);
    - 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;
    - Serum creatinine less than/equal to 1.5 times IULN Patients must have an International Normalized Ratio (INR) less than/equal to 1.5 and a Partial Thromboplastin Time (PTT) less than/equal to 1.5 IULN

- 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 150/100), on a stable regimen of anti-hypertensive therapy.

Exclusion criteria

- Prior systemic targeted therapy for mCRC
- 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 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 prophylactic use of heparin with low molecular weight is acceptable)
- Proteinuria exceeding 500mg/24 h
- 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 active bone fracture
- 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

Interventions

Arms	Assigned Interventions
Intervention (Arm A): FOLFIRI -3+bevacizumab (AryoGen pharmed)	Drug: FOLFIRI -3: In this group FOLFIRI-3 regimen consist of irinotecan 100 mg/m^2 over 1 hour at day 1, leucovorin 400 mg/m^2 at day 1 followed by a 46 hour 5-FU continuous infusion (2000 mg/m^2) and irinotecan 100 mg/m^2 over 1 hour at day 3 will administer. Drug: Bevacizumab (AryoGen pharmed): 5 mg/kg will administer at day 1 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.

Active Comparator (Arm B) FOLFIRI -3 + Bevacizumab (Avastin®)	Drug: FOLFIRI-3: In this group FOLFIRI-3 regimen consist of irinotecan 100 mg/m^2 over 1 hour at day 1, leucovorin 400 mg/m^2 at day 1 followed by a 46 hour 5-FU continuous infusion (2000 mg/m^2) and irinotecan 100 mg/m^2 over 1 hour at day 3 will administer. Drug: Bevacizumab (Avastin®): 5 mg/kg will administer at day 1 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

Induction treatment was administrated every 2 weeks for a maximum of 26 cycles, until disease progression, unacceptable toxicities, surgical intervention, or withdrawal of consent.

The response was defined according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Radiological response assessment was validated in a blinded fashion by an independent radiologist.

Suggested dose alterations for toxicity

❖ Diarrhea

Patients who develop diarrhea within 24 hours of treatment should be closely monitored and supportive care measures (e.g., fluid and electrolyte replacement, loperamide, antibiotics, etc.) provided as needed. Do not retreat until resolution of diarrhea for at least 24 hours without anti-diarrheal medication

For patients who develop abdominal cramps and/or diarrhea within 24 hours of treatment, administer atropine (0.5 mg IV) and premedicate with atropine during later cycles.

Reduce irinotecan dose by 20 % for patients with grade 2 or worse diarrhea during a prior treatment cycle

❖ Myelotoxicity

Delay treatment until absolute neutrophil count is >1500 cells/microL and the platelet count is >100,000/microL. United States Prescribing Information suggests irinotecan dose reduction by 25% for grade 3 or worse hematologic toxicity during a prior cycle. A different approach is used by some clinicians. If treatment is delayed for two weeks or delayed for one week on two separate occasions, the day 1 FU bolus is eliminated. With the second occurrence, reduce the FU infusion dose by 20 percent and reduce irinotecan dose to 150 mg/m^2

Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for dihydropyrimidine dehydrogenase deficiency

❖ Other toxicity

Hold treatment until less than or equal to grade 1, if grade 2; hold treatment until less than or equal to grade 2, if grade 3 or 4. Withhold FU for grade 2 or worse diarrhea, and restart at a lower dose after complete resolution.

Reduce irinotecan dose by 20% for patients with grade 3 or worse other non-hematologic toxicities during a prior treatment cycle.

For grade 3 mucositis; prophylactic ice chips may be beneficial

If there is a change in body weight of at least 10 percent, doses should be recalculated.

Outcomes

Primary outcomes

The primary end point is progression-free survival (PFS).

PFS is defined as 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

- Overall survival OS is defining as the time from date of randomization to date of death due to any cause.
- Objective Response rate (Tumor response was defined as partial and complete responses, according to the RECIST criteria).
- Monitoring of side effects
- Time of treatment failures define 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 outcomes

Safety will be assessed on the basis of reports of adverse events, laboratory-test results, and vital sign measurements. Adverse events were categorized according to the Common Toxicity Criteria of the National Cancer Institute, version .0, in which a grade of 1 indicates mild adverse events, a grade of 2 moderate adverse events, a grade of 3 serious adverse events, and a grade of 4 life-threatening adverse events.

Immunogenicity

Samples for immunogenicity assessment (antidrug antibody [ADA]) will be collected at the beginning of the first bevacizumab administration (visit 1), (visit 3), (visit 5), (visit 7), (visit 9), (visit 11), (visit 13), (visit 15), (visit17), (visit 19), (visit 21), (visit

23) and (visit 25). All patients in each treatment arm were considered evaluable for ADA response to bevacizumab. The evaluation of both arms immunogenicity used tiered strategies to detect, confirm, and characterize ADA responses. Each tiered strategy included the following elements:

- A screening assay to detect anti-bevacizumab antibodies;
- A confirmatory assay to assess the specificity of screen positive samples by competition with excess bevacizumab;
- A titration assay to determine anti-bevacizumab antibody titers for confirmed positive samples.

Serial dilutions of all confirmed positives were performed in order to estimate the magnitude of a positive response. The highest dilution that produced a signal above the screening assay cut point multiplied by the assay minimum required dilution (1:10) was deemed the end-point titer and was expressed as a dilution factor (reciprocal of the dilution). Any potential effects of ADAs on the efficacy (clinical index for efficacy) and safety (administration-related reactions [ARRs]) of bevacizumab were explored using descriptive statistics.

Termination policy

This decision is the responsibility of the scientific steering committee and must be approved by the Food and Drug Administration of Iran, the Ethics Committee of Shahid Beheshti University of Medical Sciences and the Ethics Committee of Ahwaz Jondi Shapur University of Medical Sciences.

Participant timelines

	Study Period for 52 weeks								
	Screening	Allocation	Post Allocation/intervention						
Time point	Visit0	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	Visit7	Visit8
Day	-7 to -1 days	0 day	2nd week	4th week	6th week	8th week	10th week	12th week	14th week
Informed consent	×								
Medical history	×								
Eligibility criteria	×								
Physical examination	×	×	×	×	×	×	×	×	×
Random allocation		×							
FOLFIRI- 3		×	×	×	×	×	×	×	×
Bevacizumab		×	×	×	×	×	×	×	×
LAB data (CBC, LFT.BUN/CR, U/A)		×	×	×	×	×	×	×	×
β-HCG*	×								
CEA	×						×		
Imaging (CT to evaluate metastatic status)	×						×		
Concomitant medication	×	×	×	×	×	×	×	×	×
Adverse event		×	×	×	×	×	×	×	×
Immunogenicity sampling		×		×		×		×	

*Only in Women

	Study Period for 52 weeks								
	Post Allocation / intervention								
Time point	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Day	16th week	18th week	20th week	22nd week	24th week	26th week	28th week	30th week	32nd week
Informed consent									
Medical history									
Eligibility criteria									
Physical examination	×	×	×	×	×	×	×	×	×
Random allocation									
FOLFIRI 3	×	×	×	×	×	×	×	×	×
Bevacizumab	×	×	×	×	×	×	×	×	×
LAB data (CBC, LFT.BUN/CR, U/A)	×	×	×	×	×	×	×	×	×
β-HCG*									
CEA				×					
Imaging (CT to evaluate metastatic status)				×					
Concomitant medication	×	×	×	×	×	×	×	×	×
Adverse event	×	×	×	×	×	×	×	×	×
Immunogenicity sampling	×		×		×		×		×

*Only in Women

	Study Period for 52 weeks									
	Post Allocation / intervention									Close-out
Time point	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
Day	34th week	36th week	38th week	40th week	42nd week	44th week	46th week	48th week	50th week	52nd week
Informed consent										
Medical History										
Eligibility criteria										
Physical examination	×	×	×	×	×	×	×	×	×	×
Random allocation										
FOLFIRI 3	×	×	×	×	×	×	×	×	×	
Bevacizumab	×	×	×	×	×	×	×	×	×	
LAB data (CBC, LFT.BUN/CR, U/A)	×	×	×	×	×	×	×	×	×	×
β-HCG*										
CEA	×									×
Imaging (CT to evaluate metastatic status)	×									×
Concomitant medication	×	×	×	×	×	×	×	×	×	×
Adverse Event	×	×	×	×	×	×	×	×	×	×
Immunogenicity sampling		×		×		×		×		

*Only in Women

Sample size

The primary endpoint (PFS) was assumed to be 10.7 months in both groups. By defining a 2-month shorter PFS with bevacizumab (AryoGen pharmed) than with bevacizumab (Avastin®) as the acceptance limit for non-inferiority, a non-inferiority margin of ($\delta = -2$ month) was selected. With 2:1 allocation, total sample sizes of 114, achieve 80% power to detect non-inferiority margin. The significance level of the test was targeted at 0.05 and standard deviation selected 4 months. Considering 10% losses to follow up, final sample size is 126 patients.

Recruitment

This study has two arms with 2:1 allocation and 126 patients will participate:

1. Group I: subjects will receive bevacizumab (produced by AryoGen Pharmed) IV infusion plus FOLFIRI-3 from 1st to 26th visit.
2. Group II: subjects will receive Avastin® (the reference drug, produced by Genentech/Roche) IV infusion plus FOLFIRI-3 from 1st to 26th visit.

Randomization

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 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. **Each Study's drug package for the course of a patient's treatment will have a 3-digit number similar to the randomization code (this number includes two English letters and one number, which is unique for each disease), so as long as the random code It's unique, each patient will have a unique drug package that will be completely identified with the randomized process. Regarding this, even if it is decoded for a patient, the type of drug used by other people will not be identified. Responsibility for creating random codes is the responsibility of** CRO Trial **on behalf of Dr. Hamid Hosseini).**

Allocation (concealment process)

Randomization process will not be exposed to those who are conducting the study and will be provided via telephone call for each consecutive eligible patient after the identification characteristics of each eligible patient have been recorded by the randomization center. Since the randomization code is unique, the next sequence is not predictable for site personnel. The allocation of randomization code will be performed after all inclusion criteria and none of exclusion criteria were met and signing the informed consent was done.

Blinding

Both Bevacizumab products are indistinguishable for patients and health care providers. Since the route of administration is infusion, it will be possible to make patients blind about the treatment group which they have been allocated to.

Treatment compliance

Patient education will be done to reduce the lack of adherence to treatment in each visit. Each patient has a reminder call before the visit.

Treatment discontinuation

The reasons for discontinuation of the drug should be clearly stated in the CRF. Study participants may be excluded from the study for the following reasons:

- Patient dissatisfaction
- Failure to adhere to treatment includes refusing to study drug requirements, refusing to perform the procedures listed in the study protocol or using drugs that are prohibited for the patient.
- Pregnancy or suspected pregnancy
- The occurrence of any blood, hepatic or renal complications requiring treatment discontinuation.
- The onset of any side effect that the investigator considers necessary for the patient to leave the study

- Failure to follow the patient
- If the patient needs treatment changes.

Data management

Data collection methods

Data collection will be electronic-based and the data will be recorded in eCRF. Adequate heed will be given to collect accurate and valid data. Investigators are responsible for completing the eCRF in study centers. The sites will be equipped with personal computers or tablets. Only the investigator or the person assigned by the investigator will have access to the database for data entry." Trial CRO" and sponsor is responsible to set up a regular monitoring scheme by qualified staff.

Data management

The chief investigator, principal investigators, and other personnel assigned by the investigators will be responsible for eCRF data entry. Each investigator will be given a specific username and password. The chief investigator and principal investigators must not disclose the data obtained from the study. All of the Investigators are responsible for keeping the study data safe. Sending and receiving the patients' information must be done considering safety and security procedures. "Trial" CRO and sponsor is responsible for planning a monitoring which will be conducted by qualified personnel in order to check the eCRF for discrepancies with the patient source documents. The monitors or auditors are not able to change eCRF data. However, they can make queries for blatant mistakes in data entry and the investigator is responsible for rectifying such mistakes or answering to the queries. The history of modification in eCRF data will be recorded meticulously and can be observed by the monitors or auditors.

Data monitoring

The objectives of the data quality control are:

- To ensure the existence of the patients and the respect of ethics (including signed patient informed consent)
- To detect the issues (including systematic errors) as early as possible for appropriate measures to be taken
- To ensure the validity of the data

To meet these objectives, quality control should be applied via the following activities:

The schedule of site quality control evaluation, performed by the monitoring team must be explained to the investigators at the time of site initiation and agreed upon. QC will be performed in study sites by the monitoring team who are in charge of planning for action plans to improve study site quality.
QC of the study site will be carried out during two main monitoring visits (30% and 70% of study completion) and several periodic monitoring visits throughout the study.

In every monitoring visit the following items will be evaluated according to a pre-prepared check list and the quality control report will be completed.

- eCRF forms will be assessed in terms of completeness, the quality of data entry and accordance with source data.
- Informed consent forms signed by the patient and the physician for all the patients who have gone through the screening visit
- Evaluation of key variables regarding the wrong and missing data

Statistical methods

1.1 Analysis principles

All tests of the effect of treatment on outcomes will be conducted on a per protocol basis. The intent-to-treat (ITT) patient population includes all patients who signed the informed consent form and underwent random assignment, and the per protocol set (PPS) population will be defined as the ITT population excluding patients who violated protocols to a considerable extent, including major protocol inclusion/exclusion criteria or treatment protocols. The safety population will be defined as all patients receiving at least one dose of study drugs.

Missing data & Outliers

All data collected on the CRF will be listed. Outliers will be identified by examining standard plots. Cases that visually “stand out” will be assessed for possible influence on results and conclusions by comparing results from analyses with and without the outlier(s).

1.2 Center considerations

Study center will not be adjusted for in the main analyses of the primary and secondary outcomes. Descriptive report of centers will be reported.

1.3 Multiple comparisons and multiplicity

There are not any planned multiple comparisons.

1.4 Covariate Adjustment

The primary statistical analyses for outcome variables will be unadjusted.

Statistical analysis

1.1 Trial profile

All patients who provide informed consent will be accounted for in the final statistical report. A CONSORT style flow diagram will illustrate patient progression through the trial from initial screening for eligibility to completion of the final primary outcome assessment. Number (percentage) by treatment group will be given for patients in the PPS population, reasons for study withdrawal, and major protocol deviations and violations.

1.2 Patient characteristics and baseline comparisons

Demographic and other baseline characteristics will be summarized by assigned treatment group. Categorical variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group, will be reported either in the body or a footnote in the summary table. Continuous variables will be summarized by mean and standard deviation or quartiles. The following baseline demographic and clinical characteristics will be presented by treatment group: gender, age at randomization, ECOG performance status (0, 1, 2), Primary tumor site (Colorectal, Colon, Rectal), Stage at first diagnosis (Local regional, Metastatic), Number of metastatic sites (0, 1, 2, 3, >=4), Alkaline phosphatase (Abnormal, Normal), Prior adjuvant therapy (Yes, No).

1.3 Analysis of the primary outcome

2 Main approach for analysis is per protocol also ITT analysis will have done.

PFS is the primary study end point, and is defined as the time from random assignment to the first documentation of PD (per investigator assessment), or death from any cause. Patients undergoing curative metastasectomy will be censored at the time for surgery. For the primary endpoint of PFS, the HR for bevacizumab (AryoGen pharmed) to bevacizumab (Avastin®) and its 95 % CI will be calculated to show the non-inferiority of bevacizumab (AryoGen pharmed) to bevacizumab (Avastin®), respectively. PFS will be estimated using the Kaplan–Meier

method. The 95 % CI for the median PFS will be calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). The Cox proportional hazards model will be used to estimate and construct confidence intervals for the HR.

2.1 Analysis of secondary outcomes

Secondary efficacy endpoints are overall survival (OS), response rate (RR) and time to treatment failure.

OS and time to treatment failure will be estimated using the Kaplan–Meier method and the 95 % CI for the median of these outcomes will be calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). The Cox proportional hazards model will be used to estimate and construct confidence intervals for the HR. To determine the magnitude of the treatment effects for ORR, proportion and frequency in two groups will be calculated.

2.2 Analysis of safety outcomes

Adverse events will be reported as incidence. For each SAE, data by treatment group will be summarized using frequencies and percentages. SAEs will be classified according to body system with reference to the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 18.

Monitoring

Site initiation visit

SIV will be performed to ensure that the facility and medications required for the trial are available in the study site and the investigators and staff involved in the study are aware of study objectives and GCP principles. In the initiation visit the role of the monitor, CRA, project manager, and the auditor will be defined clearly. After the introduction of the roles and responsibilities, staff will be taught the protocol details including timelines, sample size, eligibility criteria, protocol conformity, deviation, and reporting. The training should be documented. The eCRF details, ICD process, source documentation, randomization and serious adverse event reporting will be discussed and documented as well.

Site monitoring visit

Site monitoring visit will be performed to ensure the conduct of the study according to approved protocol and GCP principles. Before the trial starts, monitoring visits will be planned

for each study site and will be confirmed by the respective PI through email or letter. The monitoring visits during the study will be scheduled in order to visit when the planned recruitment of patients will be in its 30% and 70% progress. Sponsor is responsible for the 30% monitoring visit and "Trial" CRO is in charge of the 70% visit. In each visit, study elements will be monitored including source data, consent forms, trial medicinal products accountability, adverse events, protocol compliance, team qualification, and training. The monitoring report will be prepared and reported to both PI and sponsor preferably in an arranged meeting.

Study closeout

Study closeout visit will be performed to ensure the proper documentation of the data and return of the medicinal product and the equipment's related to the trial. After the last visit of the last participant, site close-out will be scheduled in a meeting and in the presence of the PI. The site close-out visit will start with a brief meeting with the PI and a decision will be made regarding the disposal of the remaining investigational medicinal product. The study documents will be available at the trial site. A copy all safety reports will remain with the PI and one copy will be rendered to the sponsor. There will be a brief closure meeting with the investigator at the site and the site close-out report will be prepared after the visit.

Adverse events

Safety will be assessed on the basis of reports of adverse events, laboratory-test results, and vital sign measurements. Adverse events will be categorized according to the Common Toxicity Criteria of the National Cancer Institute, version 4.0, in which grade 1-4 corresponds to mild, moderate, serious and life-threatening adverse events.

Any adverse event should be recorded. If the adverse effect is serious enough to require medical attention, it should be reported as soon as possible within a few days.

Scientific steering committee should be informed and it will take decisions on whether or not blinding should be removed and the patient should be excluded from the study.

In case of fatal or severe event requiring hospital admission, reporting should be prompt at the same day to the responsible officer in AryoGen pharmed Company by fax.

Studies show that this drug has some side effects:

- venous thromboembolic events
- hypertension
- bleeding
- arterial thromboembolic events

- gastrointestinal perforations
- wound healing complications
- fistula/intra-abdominal abscess
- proteinuria

Adverse Event (AE) will be described as any medical event occurring in patients who participate in the trial and do not necessarily have a causal relation with the treatment in study. Clinical manifestations which will be reported as an adverse effect include any symptom, sign (as any abnormal laboratory determination) or temporary disease associated to the use of the drug in study, whether they are or not etiologically related to it.

The medical conditions which present before the beginning of the study will only be considered as adverse events if they worsen during the study and cannot be attributable to the natural evolution of the disease.

Adverse Drug Reaction (ADR) will be defined as the harmful response to a drug and that is produced with the doses regularly used in the human being for the prophylaxis, diagnosis, treatment of diseases or to modify a physiological function [15].

It will be considered a Serious Adverse Event (SAE) any event that:

- Results in death;

- Implies a death risk;

- Requires hospitalization;

- Extends prior hospitalization;

- Results in persistent or significant incapacity;

- Produces a congenital anomaly or malformation, or

- Requires medical or surgical intervention to avoid a permanent damage.

Record and report of AE:

All the AE and ADRs will be recorded in the medical record of the patient and in the appropriate section of the CRF, and will be classified based on their severity and relation with

the treatment in study according to the Researcher's criteria and following the guidelines presented below.

AE classification based on its severity:

AE will be classified according to its severity in relation to the guidelines established in the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, published on November 27, 2017). Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

* A Semi-colon indicates ‘or’ within the description of the grade.

* Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AE classification based on its relation with the treatment in study:

In order to establish the relation between the AE or the ADR and the treatment in study, the following definitions will be considered:

Certain: A clinical event including alterations in the laboratory tests manifesting with a reasonable temporal sequence related to the administration of the drug and cannot be explained by the current disease, or by other drugs or substances. The response to the drug suppression (released; dechallenge) should be clinically plausible. The event should be final from a pharmacological point of view, using, if necessary, a conclusive re-exposure procedure.

Probable/Likely: A clinical event, including alterations in the laboratory tests manifesting with a reasonable temporal sequence related to the administration of the drug, which is unlikely to be attributed to the current disease, or other drugs and substances, and which when releasing the drug (dechallenge) a clinically reasonable response appears. No information on re-exposure (rechallenge) is required to assign this definition.

Possible: A clinical event, including alteration in the laboratory tests manifesting with a reasonable temporal sequence related to the administration of the drug, but can also be explained by the concurrent disease, or by other drugs and substances. The information regarding the release of the drug may be missing or unclear.

Unlikely: A clinical event, including alterations in the laboratory tests manifesting with an improbable temporal sequence related to the administration of the drug, and can be explained in a more plausible way by the concurrent disease, or by other drugs or substances.

Conditional/Unclassified: A clinical event, including alterations in the laboratory tests, notified as an adverse reaction, of which it is essential to obtain more data in order to make a proper evaluation, or the additional data are under examination.

Unassessable/Unclassifiable: A notification that suggests an adverse reaction, but cannot be judged because the information is insufficient or contradictory and cannot be verified or completed in its data.

WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

AEs Recording

All the undesirable and unexpected AEs that follow the administration of the drug will be accurately recorded in the medical record of the patient and in the corresponding section of the CRF. The event description should be recorded, as well as the temporal sequence regarding to the administration of the drug, its duration, the procedures performed for the diagnosis if appropriate, the results of the repeated exposure and the qualification made by the researcher as regards its severity and its relation to the administered drug.

AE Reporting Responsibilities

Principle investigator responsibilities:

- The investigator must report any SAE/R, which results in death or is life-threatening, to the sponsor and IEC within the maximum of 24 hours by fax, email or etc.

- The investigator must immediately report those SAE/Rs which are not life-threatening or do not result in death but may put subjects in danger or require intervention (medical or surgical) to prevent life-threatening outcomes. These SAE/R need to be reported to the sponsor and IEC as soon as possible but not later than seven calendar days of having taken notice of the SAE/R.

- The investigator should report to the sponsor and IEC all predictable adverse events of investigational medicinal product including for example injection site reactions, in case of patient withdrawal from study or adverse event with a greater frequency than expected.

Sponsor responsibilities:

- SUSARs which result in death, or are life-threatening; need to be reported by the sponsor as soon as possible but not later than seven calendar days, to IEC and IFDA, using CIOMS form (Suspect Adverse Reaction Report Form). A follow-up report is to be submitted within 15 calendar days.

- The sponsor must report SUSARs which are not life-threatening or do not result in death, but may put subjects in danger or require intervention (medical or surgical) to prevent life-threatening outcomes, as soon as possible but not later than 15 calendar days, to IEC and IFDA, using CIOMS form (Suspect Adverse Reaction Report Form). The follow-up report considering the relation between the investigational medicinal product and an adverse event is to be submitted as soon as possible.

- All the reports and follow-up results of SAE/R need to be reported to IFDA within maximum 15 calendar days after sponsor awareness of SAE/R.

- If the severity or frequency of predictable adverse events, for example, injection site reactions, results in patient withdrawal from the study, or in case of higher incidence than expected, the sponsor must report it to IFDA within maximum 15 calendar days.

- The sponsor must report all the information regarding the SAE and serious ADR that are reported during the course of the study and recommendations of investigators related to increasing of study risk for subjects to Food and Drug Administration of Iran within 15 calendar days.

- The sponsor must report to IFDA all recommendations from investigators about possible increased risk of adverse events or participants, within maximum 15 calendar days.

Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition;
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the monitoring team
- In case of any Serious Adverse Event brought to the attention of the investigator at any time after cessation of investigational product and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the monitoring team.

Withdrawal of patients:

Participants may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the patient
- Noncompliance, including refusal of study medical requirements, refusal of procedures as stated in the study protocol, or use of prohibited medications
- In the case of suspected pregnancy, a pregnancy test for Beta hCG will be requested, and if the test is positive, the patient will be excluded from the study
- The occurrence of an undesirable event that causes the investigator to consider the patient's exclusion from the study
- Not possible to follow the patient's condition (Loss to follow-up)
- A patient that does not receive a chemotherapy regimen for two consecutive cycles

The reason(s) for withdrawal should be stated clearly in the eCRF.

Patient Admission Criteria

Since all injections during the study are performed under the supervision of the nurse/nurses who have been trained, we will ensure that patients who are present at all injection days and whose injections are approved in the CRF, has an admission to the treatment.

Auditing

Regular auditing will be carried out to ensure strict adherence to the study protocol. the auditor will be determined and introduced to regulatory authorities by the sponsor.
The Audit reports will be prepared for the sponsor and the results will be reported to chief investigator as well.
Auditors will be responsible for:

- Regular visits to the study centers to inspect the sufficiency of existing structures and processes
- Identifying training needs of study site staff
- Making necessary arrangements to set up training courses
- Monitoring adherence to all procedures foreseen in the study protocol
- Preparing written report from each visit
- Certifying the quality and reliability of the monitoring visits during the study
- Certifying the quality and reliability of the study conduction by investigators and staff
- Certifying the quality and veracity of the data to be reported to legal bodies

Ethics and dissemination

Research ethics approval

- Ethics committee approval is mandatory for start of this study
- No patient will be recruited to this study without a signed informed consent.
- Patients will be informed that they can leave the study anytime they desire with no need for any explanation.
- To ensure the confidentiality in case a form is lost, the name and surname of the patients will not appear on any forms.
- Adverse effect report forms will be evaluated after every visit. The research team is responsible for dealing with the immediate aftermath of any adverse event regardless of the event being directly related to the medication that is being studied.
- Before initiation of the trial, it will be reviewed with IFDA. The protocol, CRF, information for patients and informed consent form will be submitted to the ethics committee of Shahid Beheshti university of medical sciences and Ahvaz Jondi Shapur

University of medical sciences, for review and approval according to international regulatory guidelines.

Consent

The investigator will thoroughly explain the purpose of the study to the patient. The patient will be provided with an information sheet and will be given sufficient time and opportunity to inquire about the details of the study and to decide whether or not to participate in the study, e.g. to give permission to use their data for investigative purposes, knowing their information will remain confidential. The informed consent form should be signed and dated by the patient and the person with whom they discuss the information regarding the consent form. The investigator will explain that the patient is completely free to refuse to give permission for his/her data to be used or to withdraw from the trial at any time and for any reason. Similarly, the investigator and/or sponsor will be free to withdraw the patient at any time for administrative reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to GCP guidelines, declaration of Helsinki and local regulation for clinical trials.

Confidentiality

All study-related information will be stored securely at the study site. To ensure confidentiality, randomization codes will be used on all the reports, gathered data, information regarding the study progress and administrative forms. All records that contain names or other personal identifiers, such as subject identification form and informed consent forms, will be stored separately from study records. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other lists which link participant's randomization code to other identifying information will be stored in a separate, locked file in an area with limited access. All laboratory and other test results will be kept strictly confidential. All counseling and blood sampling will be conducted in private rooms, and study staff will be required to preserve the confidentiality of all participants.

Amendment

Any modifications to the protocol which may impact on the conduct of the study, the potential benefit of the patient or may affect patient safety, including changes to study objectives, study design, patient population, sample size, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by chief Investigator and AryoGen Pharmed Company, and should be approved by the Ethics Committee prior to implementation and notified to the health authorities in accordance with

local regulations. Administrative changes to the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by chief Investigator and AryoGen Pharmed Company and will be documented in a memorandum.

Declaration of interests

The presence or absence of any kind of financial and or nonfinancial relationship between the sponsor and chief investigator and principal investigators (with the exemption of this study contract) should be officially declared to IFDA as a written conflict of interest letter.

Funding organization/Sponsor

Covering all expenses of the study including the physicians' contract, laboratory costs, providing 126 patients with their medication and insurance will be the responsibility of AryoGen Pharmed pharmaceutical company.

Access to data

Chief investigator, sponsor and CRO Trial will have access to full dataset. In addition, ethic committee and regulatory organizations can access to data, if needed.

Ancillary and post-trial care

Ancillary care (related to trial) will be provided by principal investigator under sponsor support for participants.

Dissemination policy

No other publication is allowed before the primary publication. Any subsequent presentation or publication ((including the sub-studies) by a study team member must be approved by the steering committee and chief Investigator and the primary publication should be cited. The final decision to publish any manuscript/ abstract/ presentation will be made by chief Investigator and the sponsor after prior notice to the "steering committee for their review and comments.

Appendices

Appendix 1: Informed consent form

Informed consent form for participation in the clinical trial design: Comparison of the efficacy and safety of bevacizumab of AryoGen Pharmed company with Avastin® (manufactured by ROCHE Company) in patients with metastatic colorectal cancer.

Mrs./Mr.…….

I hereby invite you to participate in the above-mentioned research. Research information is provided in this service sheet and you are free to participate or not in this research. You do not have to make an immediate decision and you can ask your questions from the research team to decide on it and consult with anyone you want. Before signing this consent, make sure you understand all the information in this form and all your questions have been answered.

Researcher……....

1- I know that the purpose of this study is to compare the efficacy and safety of bevacizumab of AryoGen Pharmed Company with Avastin® (manufactured by ROCHE Company) in patients with metastatic colorectal cancer.
2- I know that my participation in this research is totally voluntary and I do not have to participate in this research. I was assured that if I did not want to participate in this study, I would not be deprived of routine diagnostic and therapeutic care and my therapeutic relationship with the treatment center and the physician will not get affected.
3- I know that my cooperation in this study is that, after signing informed consent and being placed randomly in one of the groups of bevacizumab will be treated according to the following protocol:

Patients are randomized in to the two groups A and B (AryoGen pharmed bevacizumab or Avastin®) and will be treated according to the following protocol:

Bevacizumab 5 mg/kg will administer at day 1 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.

FOLFIRI-3:

FOLFIRI-3 regimen consist of irinotecan 100 mg/m^2 over 1 hour at day 1, leucovorin 400 mg/m^2 at day 1 over 2 hours, followed by a 46 hour 5-FU continuous infusion (2000 mg/m^2) and irinotecan 100 mg/m^2 over 1 hour at day 3 will administer.

These treatment cycles will be repeated every 2 weeks for 26 cycles. Also during 6 months to 1 year therapeutic evaluations will be done.

Before starting treatment, the full detail of the study, drug administration and its possible side effects have been described to me.

4- The possible benefits of my participation in this research are as follows:
By participating in this research, the cost of my medication will be free of charge, and during this study, I will be examined more carefully and precisely regarding side effects of medications by physicians. By participating in this study, I can help improve the patient's treatment process and make cheaper drugs being available for patients like me.

5- The possible harms and adverse events of participation in this study are as follows:
Possible damages include side effects of medications. According to the fact that one of the study groups receives Avastin® (manufactured by Roche) is a common drug that is commonly used in many countries, including Iran, adverse events are the same as mentioned in the pharmacy books. In the other group receiving bevacizumab of AryoGen pharmed, the side effects are similar to that of the previous one and have not been seen more than the usual treatment.

6- I know that the researchers of this clinical trial keep all of my information, confidential and are only allowed to publish the general and cumulative results of this research without mentioning my name and profile.

7- I know that the Ethics Committee can have access to my information for monitoring my rights.

8- Dr. Hamid Reza Rezvani was introduced to me for answering my questions and I was told that whenever a problem or question related to participation in the above-mentioned research came to me, I can ask him. His address and phone number are given to me as follows:
Address: Taleghani Hospital, Shahid Beheshti university of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran.
Telephone: 00982122432560-9

9- I know that if during the research any physical or mental problem arose for me regarding my participation in this research, it would be the responsibility of the researcher to treat side effects and compensate the costs and expenses.

10- I know that if for any reason, the clinical trial is terminated sooner or suspended, my research organization or researcher will be notified me of this matter and they ensured me that appropriate treatment and follow up will be done for me.

11- I know that if I become hospitalized due to participation in this study, or a disability or any other unpleasant consequence occur for me in this study, that if I did not attend this study, it would not happen for me, the relevant compensation is AryoGen pharmed company responsibility and I am insured by the AryoGen pharmed company due to the adverse events occur for me because of my participation in the study.

I know that if I have a problem or objection to executers of the research or the research process, I can contact the Ethics Committee of Shahid Beheshti University of Medical Sciences at the address of: Shahid Beheshti university of medical sciences, Shahid Arabi St., Yaman St., Chamran highway, Tehran, Iran and present my problem either verbally or in writing.

12- This form of information and informed consent is provided in two copies and will be signed by the researcher and me. A signed copy will be given to me and a signed copy will be given to the researcher.

I read and understood the above-mentioned tips, and based on that, I declare my informed consent to participate in this research.

Participant signature:

I consider myself bound to comply with the obligations of the executor in the above provisions, and I undertake to work on the rights and safety of people participating in this research.

Researcher signature:

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Appendix 2: RECIST

RECIST

In the terminology of RECIST, "lesion" is generally used instead of "tumour." And the lesion would be divided in to two categories, target lesion and non-target lesion. Target lesions are lesions that have been specifically measured. Non-target lesions are lesions whose presences have been noted, but whose measurements have not been taken.

Evaluation Criteria for Target Lesions

At the beginning of an evaluation, certain lesions are measured in order to provide bases for comparison. Response assessment and evaluation criteria for target lesions are as follows:

Complete Response, or CR – Signifies that all target lesions have disappeared during the course of treatment.

Partial Response, or PR – Signifies that decreases of at least 30% have been noted in the lesion that has the largest diameter, or LD.

Stable Disease, or SD – Signifies that there has been no significant decrease or increase in the size of target lesions, based on the smallest sum LD.

Progressive Disease, or PD – Signifies that there has been an increase of at least 20% in the sum of the LD of targeted lesions.

Evaluation Criteria for Non-Target Lesions

The criteria for non-target lesions are similar to those of target lesions:

- Complete Response, or CR – Signifies the disappearance of all non-target lesions.
- Stable Disease, or no CR/no PD – Signifies the continued presence of one or more non-target lesions.

- Partial Response, or PD – Signifies that appearance of at least one new lesion, or the increasing size of at least one existing non-target lesion.

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