



G.O.N.O.

GRUPPO ONCOLOGICO NORD-OVEST

**FIRST-LINE FOLFOXIRI PLUS BEVACIZUMAB FOLLOWED BY
REINTRODUCTION OF FOLFOXIRI PLUS BEVACIZUMAB
AT PROGRESSION *versus* FOLFOX PLUS BEVACIZUMAB
FOLLOWED BY FOLFIRI PLUS BEVACIZUMAB
AT PROGRESSION IN FIRST- AND SECOND-LINE TREATMENT
OF UNRESECTABLE METASTATIC COLORECTAL CANCER**

THE TRIBE-2 PHASE III STUDY

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LIST OF ABBREVIATIONS AND ACRONYMS

5-FU: 5-fluorouracil
ACE: Angiotensin-Converting-Enzyme
ADR: Adverse Drug Reaction
AE: Adverse Event
AESI: Adverse Events of Special Interest
ALAT (SGPT): Alanine-Aminotransferase (Sèrum Glutamic Pyruvic Transaminase)
APTT: Activated Partial Thromboplastin Time
ASAT (SGOT): Aspartate-Aminotransferase (Sèrum Glutamic Oxaloacetic Transaminase)
Bas: At baseline
Bev: bevacizumab
CA19.9: Carbohydrate Antigen 19.9
CAPOX: Capecitabine, Oxaliplatin
CEA: CarcinoEmbryonic Antigen
CHF: Congestive Heart Failure
CNS: Central Nervous System
CR: Complete Response
CT: Computed Tomography
CTCAE: Common Terminology Criteria for Adverse Events
CVAD: Central Venous Access Device
DPYD: Dihydropyrimidine dehydrogenase
e.g.: Example given
EC: Ethics Committee
ECG: Electrocardiography
ECOG PS: Eastern Cooperative Oncology Group – Performance Status
e-CRF: electronic Case Report Form
EDTA: Ethylenediaminetetraacetic acid
EGFR: Epidermal Growth Factor Receptor
ELISA: Enzyme Linked Immunosorbent Assay
EOR: Early Objective Response
ERCC1: Excision Repair Cross-Complementation group 1
FOLFIRI: folinic-acid, 5-Fluorouracil, irinotecan
FOLFOX: folinic-acid, 5-Fluorouracil, oxaliplatin
FOLFOXIRI: folinic-acid, 5-Fluorouracil, oxaliplatin, irinotecan
G-CSF: Granulocyte – Colony Stimulating Factor
GI: Gastrointestinal
GONO: Gruppo Oncologico Nord-Ovest
GISCAD: Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente
HR: Hazard Ratio
ICH: International Conference on Harmonisation
INR: International Normalized Ratio
ISBN: International Standard Book Number
ITT: Intension To Threat

LDH: Lactate Dehydrogenase
LOHP: oxaliplatin
LV: leucovorin
mCRC: metastatic colorectal cancer
MRI: Magnetic Resonance Imaging
NA: Not Available
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
NCIC-CTG: National Cancer Institute of Canada – Clinical Trials Group
NYHA: New York Heart Association
ORR: Overall Response Rate
OS: overall survival
pCR: pathologic Complete Response
PD: Progression Disease
PDGF: Platelet-derived Growth Factor
PFS: Progression Free Survival
PIGF: Placental Growth Factor
PR: Partial Response
PRES/RPLS: Posterior Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome
RECIST: Response Evaluation Criteria In Solid Tumors
RR: response rate
SADR: Serious Adverse Drug Reaction
SAE: Serious Adverse Event
SBP: Survival Beyond Progression
SC: Subcutaneously
SNP: Single Nucleotide Polymorphism
SP: Safety Population
sVEGFRs: soluble Vascular Endothelial Growth Factor Receptor 2
TE: Tracheoesophageal
TFS: Time to Failure of Strategy
TP: Thymidylate Phosphorylase
TS: Thymidylate Synthase
TTP: Time To Progression
UGT1A: UDP glucuronosyltransferase 1 A
ULN: Upper Limit of Normal
UNL: Upper-Normal Limits
VEGF: Vascular Endothelial Growth Factor
VEGFRs: VEGF receptors
WBC: White Blood Cell
Wks: weeks
XPD: Xeroderma Pigmentosum D

1. INTRODUCTION

1.1. FOLFOXIRI plus bevacizumab as first-line treatment of unresectable mCRC

A growing amount of drugs is indicated for the first-line treatment of mCRC and, in the absence of contraindications, the association of a biologic agent to a chemotherapy backbone is a standard choice as a first-line regimen. The intensity of the upfront chemotherapy is a highly debated issue and international guidelines [1,2] include one- to three-drugs regimens as possible options according to the treatment's objective (conversion vs palliative intent), disease's characteristics (indolent vs aggressive behaviour, tumor load) and patient's general conditions and comorbidities. Not only the three conventional cytotoxics (fluoropyrimidines, oxaliplatin, irinotecan), but also three targeted agents (the anti- Vascular Endothelial Growth Factor (VEGF), bevacizumab (bev) and the anti-Epidermal Growth Factor (EGFR) monoclonal antibodies, cetuximab and panitumumab) can be used in the first-line setting. Phase III randomized trials demonstrate that the addition of the antiangiogenic bev to first-line fluoropyrimidine-based monochemotherapy [3-5] as well as to oxaliplatin- [6] or irinotecan-based doublets [7] provided a significant benefit in terms of survival. Metanalyses estimating the magnitude of this benefit consistently show a reduction of the risk of death around 20% [8-10].

Bev safety profile is now well-known and easily manageable. Phase IV BEAT, BRiTE and ARIES trials included more than 5000 patients treated in the daily practice with chemotherapy plus bev and indicate that the incidence of bev-related adverse events is quite low and includes bleeding (3%), gastrointestinal perforation (1-2%), arterial thromboembolism (1-2%), hypertension (5-8%), proteinuria (1%) and wound-healing complications (1-2%) [11-13].

More recently, a phase II trial by the G.O.N.O. group evaluated the combination of bev with the three-drugs regimen FOLFOXIRI (CPT-11 165 mg/sqm d1, LOHP 85 mg/sqm d1, LV 200 mg/sqm d1 and 5-FU 3200 mg/sqm infusion over 48h). Cycles were repeated every 2 weeks, for a total of 12 cycles, followed by a maintenance treatment with 5-FU/LV and bev. According to a Phase II single-stage Fleming design, assuming

a null hypothesis of 10 months-progression free rate (10m-PFR) of 50% and an alternative hypothesis of 10m-PFR of 70%, with alpha and beta-errors of 0.05 and 0.10, the experimental treatment would have been judged to be promising if at least 33 patients, out of 53 evaluable, had been free of progression at 10 months.

At a median follow-up of 28.8 months, 42 (74%) out of 57 treated patients were actually free of progression at 10 months, with a median PFS of 13.1 months and a median OS of 30.9 months. In terms of activity, promising results were reported, with a RR of 77% and a disease control rate of 100%. Such a considerable activity translated into a radical resection rate of 26%, rising to 40% among patients with liver-only metastases. A pCR was observed in 20% of patients who underwent radical resection. The safety profile was absolutely consistent with expected toxicities and no unforeseen adverse events were reported [14].

Based on these promising findings the phase III TRIBE trial was designed. Five-hundred-eight unresectable mCRC patients were randomly assigned to receive up to 12 cycles of FOLFOXIRI plus bev or FOLFIRI plus bev, both followed by 5FU/LV plus bev until disease progression. Primary endpoint was PFS. Patients treated with FOLFOXIRI plus bev achieved a significantly longer PFS (12.1 vs 9.7 months, stratified HR: 0.75 [0.62-0.90], p=0.003) and a higher response rate (65% vs 53%, p=0.006). No significant differences in terms of secondary resection rate with radical intent were observed (26% vs 21%, p=0.327). A preliminary analysis, at a median follow up of 32.2 months, evidenced a trend toward longer OS in the experimental arm (31.0 vs 25.8 months, stratified HR: 0.79 [0.63-1.00], p=0.054).

The safety profile was consistent with results from the previous phase III trial by the G.O.N.O. group of FOLFOXIRI vs FOLFIRI. The triplet was associated with increased grade 3/4 neutropenia (50% vs 20%), diarrhea (19% vs 11%) and stomatitis (9% vs 4%) but not with higher incidence of febrile neutropenia (9% vs 6%). Bev-related adverse events were in the expected range. The incidence of serious adverse events (20.4% vs 19.7%) and treatment-related deaths (2.4% vs 1.6%) was not significantly different between treatment arms [15].

Previous impressive results achieved by the triplet FOLFOXIRI in terms of activity and secondary resections led to consider such an intensive upfront regimen as a preferable choice also when a remarkable tumor shrinkage is needed. Indeed, this suggestion has been recently confirmed by phase II OLIVIA trial [16], that randomized 80 mCRC patients with liver-only metastases, defined as initially unresectable by a multidisciplinary team, to receive FOLFOX plus Bev or FOLFOXIRI plus Bev. Overall (R0/R1/R2) resection rate, the primary endpoint, was numerically higher in the FOLFOXIRI plus bev arm (61.0% vs 48.7%, $p=0.271$). The triplet plus bev allowed to achieve an higher R0 resection rate (48.8% vs 23.1%, $p=0.017$) and an impressively higher ORR (80.5% vs 61.5%, $p=0.061$), with a substantial benefit also in terms of PFS (18.8 vs 12.0 months, $p=0.0002$).

1.2. Continuation of bevacizumab beyond progression in mCRC

More than ten years ago, preclinical experiences suggested the potential efficacy of a sustained antiangiogenic strategy beyond the first occurrence of resistance. Results from the observational studies BRiTE and ARIES provided initial clinical data in support of this hypothesis. In particular, in the large US prospective observational cohort study BRiTE 642 (44.4%) out of 1445 patients who had experienced progressive disease, received bev beyond progression, while 531 (36.7%) received no bev beyond progression [12]. A significant advantage in terms of survival beyond first progression (SBP) was noted with this strategy, that was still significant after adjusting for other prognostic factors (HR:0.49 [0.41-0.58], $p<0.001$). Similar results were provided by the ARIES observational study. Among 539 out of 1097 patients who received bev beyond progression significantly longer SBP was observed, compared to 417 patients who did not. Results provided by the multivariate model were consistent with those from BRiTE trial (HR: 0.41 [0.34-0.49], $p<0.001$) [17].

More recently, a phase III trial, named TML (Treatment across Multiple Lines - ML18147) was conducted in Europe and Saudi Arabia, randomizing mCRC patients previously treated with bev plus standard first-line chemotherapy to cross-over

chemotherapy with or without bev. Enrolled patients had experienced progressive disease less than 4 weeks prior to start of study treatment. Primary endpoint was OS. The use of bev beyond progression provided a significant advantage in terms of OS (11.2 vs 9.8 months, HR: 0.81 [0.69-0.94], $p=0.0062$) and PFS (5.7 vs 4.1 months, HR: 0.68 [0.59-0.78], $p<0.0001$), while no differences in response rate were reported (5.4% vs 3.9%, $p=0.311$). Adverse events were consistent with the expected toxicity profile of bev. As expected, the advantage provided by the addition of bev was independent of the *KRAS* mutational status [18-19].

Another phase III study with a similar design, the BEBYP (Bevacizumab BeYond Progression) trial, was contemporaneously conducted in Italy and prematurely stopped when results from TML were released. Primary endpoint was PFS. The continuation of bev beyond progression provided a significant advantage in terms of PFS (6.8 vs 5.0 months, HR: 0.72 [0.54-0.97], $p=0.0029$), while no differences in response rate (21% vs 18%, $p=0.71$) or OS (14.1 vs 15.5 months, HR: 0.77 [0.56-1.07], $p=0.12$) were reported. Nevertheless, the trial was clearly underpowered to detect an advantage in terms of survival [20].

Consistent results from both trials demonstrated the efficacy of a prolonged antiangiogenic strategy and identified the prosecution of bev in combination with a switched chemotherapy as a reasonable option for the second-line treatment of mCRC patients who have already received a bev-containing first-line regimen.

1.3. Induction and maintenance phases in the era of targeted agents

Recent evidences point out the correlation of the early objective response with survival in mCRC, thus highlighting the potential influence of the early tumor shrinkage on the subsequent steps of disease history. These findings also underscore the importance of achieving a relevant tumor shrinkage early after an intensive upfront treatment.

At the same time, the optimal duration of chemotherapy and Bev is still a matter of debate and some trials indicate that the possibility to alternate on-chemo and chemo-

free intervals is a reasonable option. Phase III randomized OPTIMOX1 (21), 2 (22), COIN (23) and GISCAD (24) trials addressed this issue, substantially evidencing that the choice not to continuously administer the treatment until the evidence of disease progression, but to alternate periods of less intensive chemotherapy or chemo-holidays can be pursued without compromising patients' prognosis.

Nowadays, in the targeted agents' era, a heated issue concerns the importance of the so called "maintenance" treatment, that is the choice to pursue the antiangiogenic until disease progression, also in the case of a partial or total interruption of the associated chemotherapy. SAKK 41/06 study is a non-inferiority trial that randomized 262 patients that did not progress after 4-6 months of chemotherapy plus Bev, to continue or not Bev alone until disease progression. The non-inferiority of the observation strategy was not demonstrated in terms of time to progression (TTP) or OS. Patients treated with Bev reported a 1.2 months absolute advantage in TTP (4.1 vs 2.9 months from randomization, HR: 0.74 [0.57-0.95], p for non-inferiority=0.470) and a 3.3 months advantage in OS (26.1 vs 22.8 months, HR: 0.83 [0.61-1.12], p for difference=0.218) (25).

In CAIRO-3 trial, patients achieving a disease stabilization or response after six cycles of CAPOX plus Bev were randomized between observation or maintenance treatment with capecitabine plus Bev. Upon the first disease progression, CAPOX plus bev had to be reintroduced and continued until the second evidence of disease progression. The primary endpoint was the PFS2, defined as the time from randomization to progression upon re-introduction of CAPOX plus bev. Patients in the maintenance arm achieved a significant benefit in terms of PFS2 (11.8 vs 10.5 months, HR: 0.81 [0.67-0.98], p=0.028), PFS (8.5 vs 4.1 months, HR: 0.44 [0.36-0.53], p<0.00001) and a non-significant advantage in OS (21.7 vs 18.2 months, HR: 0.87 [0.71-1.06], p=0.156) that becomes significant in the adjusted analysis (HR: 0.80, p=0.035) (26).

On the basis of these evidences, the opportunity to alternate induction and maintenance phases in the disease history of mCRC patients is considered a valuable option.

2. STUDY RATIONALE

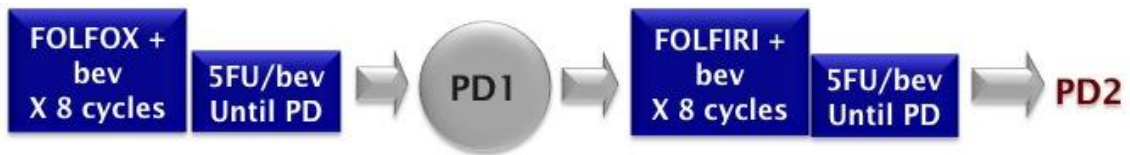
- Bev improves the efficacy of first-line chemotherapy in unresectable mCRC.
- In the phase III TRIBE trial upfront FOLFOXIRI plus bev provided a significant advantage in terms of PFS and RR compared to FOLFIRI plus bev. A trend toward better OS was also evidenced. The second-line treatment was at investigator's choice. A manageable increase in diarrhea, mucositis and neutropenia was reported, while no differences in febrile neutropenia, serious adverse events and toxic deaths were evidenced.
- A growing amount of data support the clinical relevance of achieving an early and deep tumor shrinkage.
- Phase III TML and BEBYP trials demonstrated that the continuation of bev beyond disease progression combined with a switched chemotherapy regimen provided a significant advantage in terms of OS and PFS.
- Based on recent evidences, the partial interruption of the upfront "induction" chemotherapy before disease progression and the prosecution of bev until disease progression as maintenance treatment is a valid strategy in the treatment of mCRC.

On the basis of these considerations, a first-line doublet plus bev followed by a second-line switched doublet (from oxaliplatin to irinotecan and viceversa) plus bev should be considered a standard option for mCRC patients. Only retrospectively collected data are currently available about the efficacy of first-line FOLFOXIRI plus bev followed by second-line rechallenge with FOLFOXIRI plus bev. We therefore designed the present phase III randomized trial of first-line FOLFOXIRI plus bev followed by reintroduction of FOLFOXIRI plus bev at progression versus FOLFOX plus bev followed by FOLFIRI plus bev at progression in first- and second-line treatment of unresectable mCRC patients.

3. STUDY DESIGN

This is a prospective, open-label, multicentric phase III randomized trial in which initially unresectable and previously untreated mCRC patients will be randomized to receive:

Arm A:



OR

Arm B:



The third- and subsequent lines of treatment will be at investigators' choice.

4. STUDY OBJECTIVES

4.1. Primary objective

The main objective of this trial is to compare the efficacy of the two proposed treatment strategies in terms of duration of Progression Free Survival 2 (PFS2).

4.2. Secondary objectives

Secondary objectives of this study are to compare the two proposed treatment strategies in terms of:

- Duration of Progression Free Survival (PFS);
- Duration of 2nd-Progression Free Survival (2nd-PFS);
- Duration of Time to Failure of Strategy (TFS);
- Duration of Overall Survival (OS);
- Distribution of Objective Response Rate (ORR) during first- and second-line treatment;
- Distribution of Early Objective Response (EOR) during first-line treatment;
- Distribution of the rate of secondary R0 resection of metastases;
- Safety profile;
- Translational analyses.

5. PATIENTS' SELECTION

5.1. Inclusion criteria

- Histologically proven diagnosis of colorectal cancer
- Initially unresectable metastatic colorectal cancer not previously treated with chemotherapy for metastatic disease
- At least one measurable lesion according to RECIST1.1 criteria
- Availability of a tumoral sample
- Male or female of 18-75 years of age
- ECOG PS \leq 2 if aged $<$ 71 years, ECOG PS = 0 if aged 71-75 years
- Life expectancy of at least 12 weeks
- Previous adjuvant chemotherapy allowed only if with fluoropyrimidine monotherapy and more than 6 months elapsed between the end of adjuvant and first relapse
- Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hgb >9 g/dl
- Total bilirubin 1.5 time the upper-normal limits (UNL) of the normal values and ASAT (SGOT) and/or ALAT (SGPT) $<2.5 \times$ UNL (or $<5 \times$ UNL in case of liver metastases) alkaline phosphatase $<2.5 \times$ UNL (or $<5 \times$ UNL in case of liver metastases)
- Creatinine clearance >50 mL/min or serum creatinine $1.5 \times$ UNL
- Urine dipstick of proteinuria $<2+$. Patients discovered to have 2+ proteinuria on dipstick urinalysis at baseline, should undergo a 24-hour urine collection and must demonstrate <1 g of protein/24 hr
- Women of childbearing potential must have a negative blood pregnancy test at the baseline visit. For this trial, women of childbearing potential are defined as all women after puberty, unless they are postmenopausal for at least 12 months, are surgically sterile, or are sexually inactive.
- Subjects and their partners must be willing to avoid pregnancy during the trial and until 6 months after the last trial treatment. Male subjects with female partners of childbearing potential and female subjects of childbearing potential must, therefore,

be willing to use adequate contraception as approved by the investigator (barriere contraceptive measure or oral contraception)

- Will and ability to comply with the protocol
- Written informed consent to study procedures and to molecular analyses.

5.2. Exclusion criteria

- Radiotherapy to any site within 4 weeks before the study
- Previous adjuvant oxaliplatin-containing chemotherapy
- Previous treatment with bevacizumab
- Untreated brain metastases or spinal cord compression or primary brain tumours
- History or evidence upon physical examination of CNS disease unless adequately treated
- Symptomatic peripheral neuropathy > 2 grade NCIC-CTG criteria
- Serious, non-healing wound, ulcer, or bone fracture
- Evidence of bleeding diathesis or coagulopathy
- Uncontrolled hypertension and prior history of hypertensive crisis or hypertensive encephalopathy
- Clinically significant (i.e. active) cardiovascular disease for example cerebrovascular accidents (≤ 6 months), myocardial infarction (≤ 6 months), unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication
- Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of study enrolment.
- Any previous venous thromboembolism > NCI CTCAE Grade 3.
- History of abdominal fistula, GI perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to the first study treatment.
- Current or recent (within 10 days prior to study treatment start) ongoing treatment with anticoagulants for therapeutic purposes

- Chronic, daily treatment with high-dose aspirin (>325 mg/day)
- Treatment with any investigational drug within 30 days prior to enrollment or 2 investigational agent half-lives (whichever is longer)
- Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of localized basal and squamous cell carcinoma or cervical cancer in situ
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study
- Lack of physical integrity of the upper gastrointestinal tract, malabsorption syndrome, or inability to take oral medication
- Pregnant or lactating women. Women of childbearing potential with either a positive or no pregnancy test at baseline. Postmenopausal women must have been amenorrheic for at least 12 months to be considered of non-childbearing potential. Sexually active males and females (of childbearing potential) unwilling to practice contraception (barriere contraceptive measure or oral contraception) during the study and until 6 months after the last trial treatment.

5.3 Discontinuation Criteria

A patient may be discontinued from the clinical trial at any time for any reason.

It is the right and the duty of the investigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, patients have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. In instances where consent is withdrawn, the Investigator must clarify whether the patient is willing to continue to be followed (i.e. for survival).

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Any medical condition that at the judgement of the Investigator or of the Sponsor may jeopardise patient's safety if he or she continues on study treatment;
- Major protocol violation (i.e. affecting the patients' safety);
- Investigator or Sponsor determines it is in the best interest of the patient;
- Patient's non-compliance to the protocol;
- Patient withdrawal of consent.

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent;
- Patient lost to follow-up;
- Death.

5.4 Replacement of Subjects

A subject who discontinues from the trial will not be replaced.

6. PARTICIPATING CENTERS, ENROLLMENT AND STUDY TIMELINE

About 60 Italian Oncology Units will participate to the trial. 654 patients will be randomized.

The registration and randomization procedures will be centralized at Clinical Trials Coordinating Center - Istituto Tosca+++no Tumori.

Patients considered eligible and who have signed a written informed consent will be randomly assigned to one of the two treatment arms in a 1:1 ratio. Eligible patients will be stratified according to center, ECOG PS (0 vs 1, 2), primary tumor location (right vs left or rectum) and previous adjuvant chemotherapy (yes vs no).

The randomization will be performed by using an electronic WEB-based system.

The randomization code will consist of a unique identification code. This code must be used on all further documentation and correspondence, including electronic case record forms (e-CRFs). e-CRFs fac-simile are provided as a separate addendum to this study protocol.

It is responsibility of the principal investigator to ensure that each patient is eligible for the study before requesting randomization.

Study length is planned to be about 4.5 years since the enrollment is expected to be about 3 years, with a minimum period of follow-up of 18 months.

The end of study is defined as the time when all randomized patients will have experienced the second evidence of disease progression or will be out of treatment as per protocol, toxicity or medical decision.

The planned study timeline is as follows:

1. Submission date to health authority / ethics: November 2014
2. First Patient In: December 2014
3. Enrollment rate: 200 pts/year
4. Last Patient In: December 2017
5. Last Patient Last Visit: May 2019

6. Preliminary data on ORR and safety will be reported with no comparative intent when 150, 300 and 450 patients will have been randomized. This will happen approximately after 18, 27 and 36 months from the first patient in, respectively.
7. Efficacy interim analysis on primary endpoint: after 303 events (early 2018)
8. First data release on PFS2: Early 2020
9. Manuscript submission: Late 2020

7. STUDY TREATMENT AND PROCEDURES

7.1. Study treatment

Eligible patients will be randomized to receive:

Arm A

mFOLFOX-6 plus bev

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Oxaliplatin 85 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluoruracil 400 mg/sqm iv bolus, day 1
- 5-fluoruracil 2400 mg/sqm 48 h-continuous infusion, starting on day 1

to be repeated every 2 weeks for a maximum of 8 cycles.

If no progression occurs, patients will receive maintenance **5-FU/LV plus bev** at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal.

The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluoruracil because of adverse events, patient's refusal or investigator's choice.

At the time of disease progression patients will receive **FOLFIRI plus bev***

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Irinotecan 180 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluoruracil 400 mg/sqm iv bolus, day 1
- 5-fluoruracil 2400 mg/sqm 48 h-continuous infusion, starting on day 1

to be repeated every 2 weeks for a maximum of 8 cycles.

*Doses may be modified according to patient's tolerance to 1st-line regimen.

If no progression occurs, patients will receive maintenance **5-FU/LV plus bev** at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal.

The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluorouracil because of adverse events, patient's refusal or investigator's choice.

Arm B:

FOLFOXIRI plus bev

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Irinotecan 165 mg/sqm iv over 60 minutes, day 1
- Oxaliplatin 85 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluorouracil 3200 mg/sqm 48 h-continuous infusion, starting on day 1

to be repeated every 2 weeks for a maximum of 8 cycles.

If no progression occurs during FOLFOXIRI plus bev, patients will receive maintenance 5-FU/LV plus bev at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal.

The prosecution of bev until disease progression is recommended also if 5-fluorouracil is interrupted because of adverse events, patient's refusal or investigator's choice.

At the time of disease progression, patients will re-introduce FOLFOXIRI plus bev at the same doses and schedule previously tolerated, for a maximum of 8 cycles. In the case of persistent neurotoxicity \geq G2, FOLFIRI plus bev will administered for a maximum of 8 cycles.

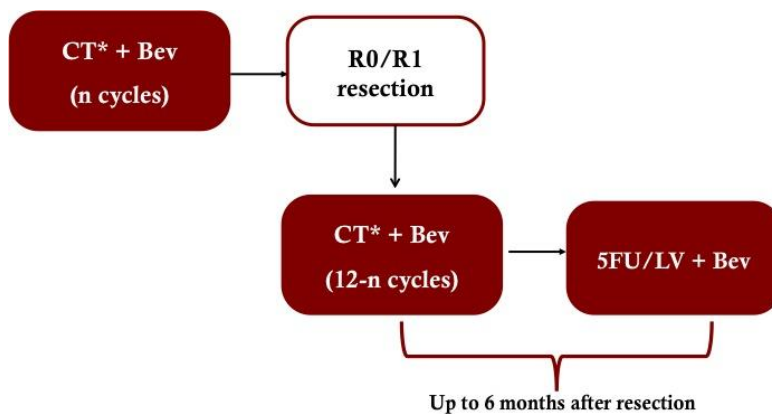
If no progression occurs during FOLFOXIRI plus bev, patients will receive maintenance 5-FU/LV plus bev at the same dose used in the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal.

The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluorouracil because of adverse events, patient's refusal or investigator's choice.

7.2. Secondary resection of metastases

Surgical radical resection of residual metastases in responsive patients is highly recommended and its feasibility should be evaluated every 2 months. It is strongly recommended to assess patients' resectability in the frame of a multidisciplinary group with a good expertise in the management of mCRC.

At least 5 weeks should elapse between the last administration of bev and the day of surgery. After resection, patients will receive post-operative therapy for 6 months (12 cycles) possibly up to 12 cycles of the same chemotherapy plus Bev regimen received before resection followed by 5FU/LV plus bev up to a total of 12 post-operative cycles (including chemotherapy plus Bev and 5FU/LV plus Bev). Post-operative treatment should start not earlier than 4 weeks after surgery. In the case of repeated procedures, post-operative treatment should start not earlier than 4 weeks after the last procedure. The choice to administered additional cycles of systemic treatment between two procedures of a pre-planned 2 stage-surgery is at investigator's choice.



* According to treatment arm

If disease progression occurs more than 1 year after the completion of the post-operative therapy, the second-line treatment according to the randomization arm is still recommended but it will be considered out of study .

7.3. Baseline and on treatment clinical evaluations

At baseline:

- Medical history, ECOG PS, physical examination (including height and weight, blood pressure and heart rate);
- ECG;
- Complete blood examination: blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium), International normalized ratio (INR)/Activated partial Thromboplastin Time (APTT), CEA, CA19.9; pregnancy test (if clinically indicate);
- Urinalysis;
- Contrast-Enhanced chest and abdominal CT scan, or Abdomen MRI and Chest CT if contrast-enhanced CT scan is contraindicated. To be performed no more than 28 days before randomization;

- Collection of a copy of baseline CT scan (and/or abdomen MRI), digitally stored on CD-ROM;
- Obtained written informed consent;
- Collection of a paraffin-embedded block of the primary tumor and/or metastases, or 10 slides 5 µm-thick for immunohistochemistry and 10 slides 8 µm-thick;
- Collection of blood and plasma samples.

Before every cycle of treatment (induction or maintenance), until the 2nd evidence of PD:

- Partial blood examination: Blood count and differential, bilirubin (total and direct), serum creatinine, INR/APTT (only for patients on anticoagulation therapy);
- Dipstick proteinuria;
- Collection of reported adverse events;
- ECOG PS, physical examination (including height, weight, blood pressure and heart rate).

Every 8 weeks until the 2nd evidence of PD:

- Complete blood examination: Blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium), INR/APTT, CEA, CA19.9;
- Contrast-Enhanced chest and abdominal CT scan, or Abdomen MRI and Chest CT if contrast-enhanced CT scan is contraindicated (the same technique used in the baseline assessment);
- Collection of blood and plasma samples.

At the end of the treatment and after the 2nd evidence of PD (visits scheduled according to investigator's practice):

- ECOG PS, physical examination (including height, weight, blood pressure and heart rate);

- Follow up on adverse events still ongoing at the time of 2nd PD;
- Survival follow up.

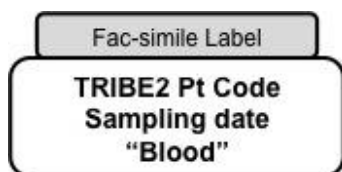
7.4. Tissue specimens collection

The collection of tissue specimens is mandatory for study entry. A paraffin-embedded block of the primary tumor and/or metastases if available, or 10 slides 5 μm -thick for immunohistochemistry and 10 slides 8 μm -thick for molecular biology analyses, are required.

Tissue specimens will be sent, together with the accompanying histological report, to the Coordinating Center (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana), where they will be collected and adequately stored under the responsibility of Dr. Loupakis.

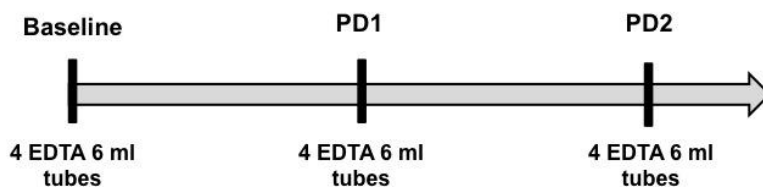
7.5. Blood sampling collection

Three 6ml EDTA tubes will be collected once at anytime before or during the treatment. They will be labelled as “TRIBE2 - Patient Code/ SNP Blood” (see fac-simile) and will be stored at -20°C until shipment to the Coordinating Center (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana).



In addition, four 6 ml EDTA tubes will be collected at the following time-points:

- at baseline (Bas)
- at the first evidence of PD (PD1)
- at the second evidence of PD (PD2)

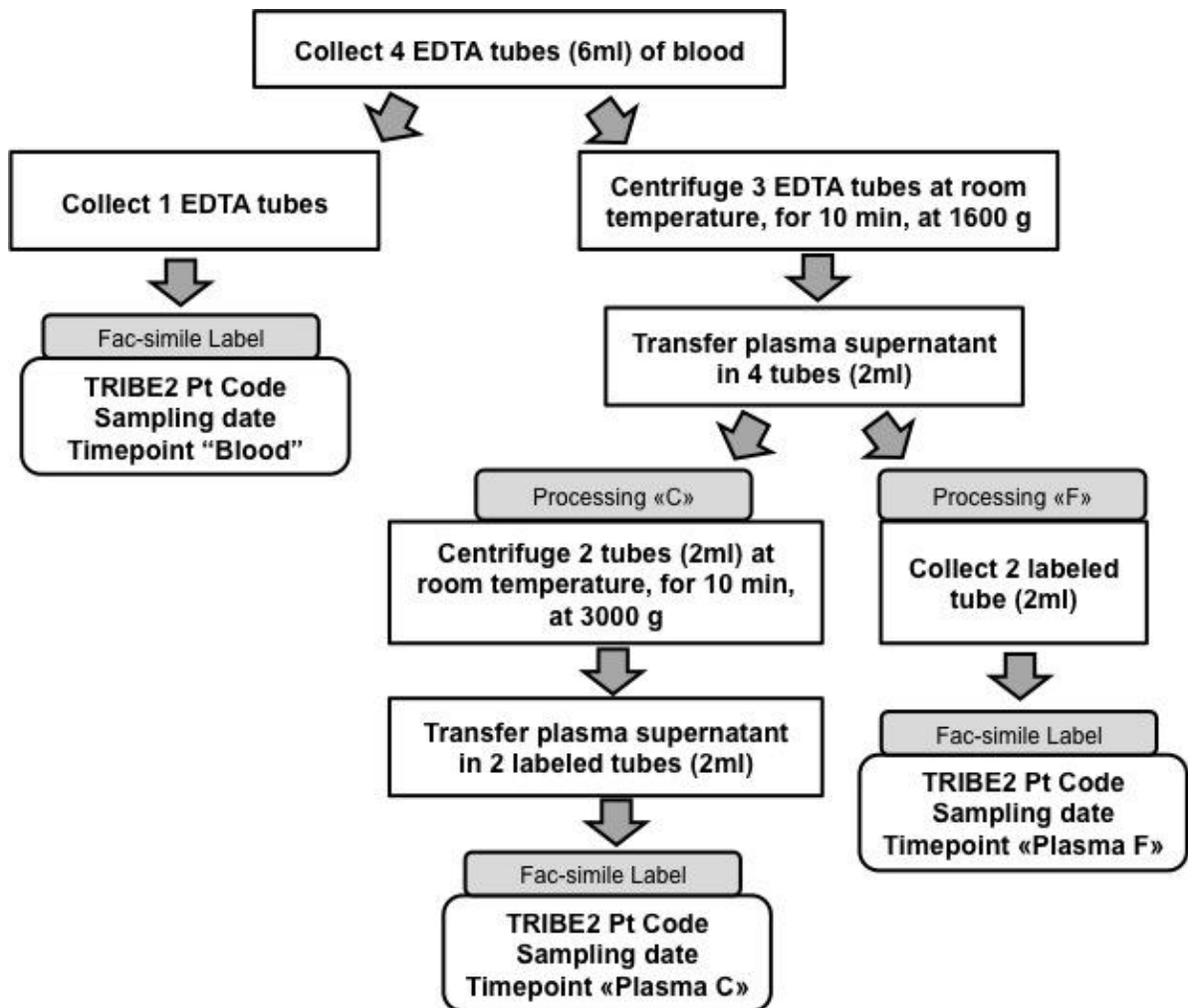


One tube will be labelled as “TRIBE2 - Patient Code/ Date/ Bas or PD1 or PD2/Blood” (see fac-simile) and directly stored at -80°C until shipment to the Coordinating Center (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana).

Three tubes will be centrifuged as soon as possible at room temperature at 1600 g x 10 minutes and plasma supernatant will be collected and divided into four aliquots. Two aliquots will be stored at -80°C until shipment to the Coordinating Center in

tubes labelled as “TRIBE2 – Patient Code/ Date/ Bas or PD1 or PD2/ Plasma F” (see fac-simile).

The other 2 aliquots will be centrifuged at room temperature at 3000 g x 10 minutes and plasma supernatant will be collected in tubes labelled as “TRIBE2 – Patient Code/ Date/ Bas or PD1 or PD2/ Plasma C” (see fac-simile).



The shipment of blood samples will be arranged by the G.O.N.O. that will provide dry ice for the shipment.

7.6. Collection of CT scan images

Tumor response will be assessed through contrast-enhanced chest and abdomen CT scans with a contiguous slice thickness of ≤ 7 mm, that will be performed in the radiology department of the study site. Abdomen MRI and chest CT scan are allowed in the case of contraindications to the use of iodine contrast agents.

In the case of clinical suspicion of disease progression, the radiographic evaluation should be performed within a maximum of 7 days to confirm objective disease progression.

CD-ROM copies of the CT scans at baseline, at the time of the best response during the first treatment, at the time of the first and second evidence of PD will be collected at the Coordinating Center (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana) for central review.

Site should follow their local privacy practices to de-identify all subject identifying information (name, medical record number, ect.) prior to submitting images to Coordinating Center.

Upon receipt, the Coordinating Center will verify that this information has been completely redacted, and, if necessary, will redact any remaining identifying information.

7.7. Tabulated overview

| Procedure | Screening (within 28 days before random) | Baseline | Before every cycle¹ | Every 8 wks¹ | After the 2nd evidence of PD |
|---|---|-----------------|---------------------------------------|--------------------------------|-------------------------------------|
| <i>Informed Consent</i> | X | | | | |
| <i>Complete medical history</i> | X | | | | |
| <i>Inclusion/Exclusion Criteria Checked</i> | X | | | | |
| <i>Tumor assessment (total-body CT or abdomen MRI + chest CT)</i> | X | | | X | |
| <i>Collection of a CD-ROM copy of CT scan</i> | X | | | X | |
| <i>12-lead ECG</i> | X | | | | |
| <i>ECOG PS</i> | X | X | X | X | |
| <i>Physical examination</i> | X | | X | X | |
| <i>Complete blood examination²</i> | X | | | X | |
| <i>Partial blood examination³</i> | | X | X | | |
| <i>Dipstick proteinuria</i> | X | X | X | | |
| <i>Collection of a paraffin-embedded tissue sample</i> | X | | | | |
| <i>Collection of blood samples</i> | | X | | X⁴ | |
| <i>Adverse events and toxicity</i> | | | X⁵ | | X⁶ |
| <i>Survival follow up</i> | | | | | X |

1. Until the 2nd evidence of disease progression

2. Blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium), International normalized ratio (INR)/Activated partial Thromboplastin Time (APTT), CEA, CA19.9; pregnancy test (if clinically indicate);

3. Blood count and differential, bilirubin (total and direct), serum creatinine, INR/APTT (only for patients on anticoagulation therapy);

4. Only at the first and second evidence of PD

5. AE assessment to be started after signing of IC until 30 days after last study treatment

6. Follow up on adverse events still ongoing at the time of 2nd PD

8. SAFETY ISSUES

8.1. Dose reductions and delays

Toxicities should be evaluated according to CTCAEv4.0. Once a dose has been reduced it should not be increased at a later time.

Dose modifications for toxicities attributable to chemotherapy

| TOXICITY AT THE START OF SUBSEQUENT CYCLES OF THERAPY | GRADE/ Values | Irinotecan | Oxaliplatin | 5FU |
|--|---------------------------|------------------------------|--------------------|-------------|
| WBC | < 3.000/mm ³ | Hold until resolution | | |
| Neutrophils | < 1.000/mm ³ | | | |
| Platelets | < 100.000/mm ³ | | | |
| Diarrhea | ≥ 1 | | | |
| Mucositis | ≥ 1 | | | |
| Any other non-hematological toxicity | ≥ 2 | | | |
| Hand/foot syndrome | 3-4 | 100% | 100% | STOP |
| Neurotoxicity | ≥ 3 | 100% | STOP | 100% |

| PREVIOUS TOXICITY | GRADE | Irinotecan | Oxaliplatin | 5FU |
|--------------------------|--------------|-------------------|--------------------|-------------|
| Neutropenia >5 days | 4 | 75% | 75% | 100% |
| Febrile Neutropenia | 4 | | | |
| Thrombocytopenia | 3-4 | | | |
| Diarrhea | 3 | 75% | 100% | 75% |
| Diarrhea | 4 | 50% | 100% | 50% |
| Stomatitis | 3 | 100% | 100% | 75% |
| Stomatitis | 4 | 100% | 100% | 50% |
| Myocardial Ischemia | NA | 100% | 100% | STOP |

Dose modifications for toxicities attributable to bevacizumab

| Event | Grade | Adjustment to bev |
|--|--|---|
| Hypertension | 3 | If not controlled by 3-drug medication, permanently discontinue |
| | 4 (Hypertensive crisis and encephalopathy) | Permanently discontinue |
| Hemorrhage | Any grade CNS | Permanently discontinue |
| | ≥2 (pulmonary) | Permanently discontinue |
| | ≥3 (non-pulmonary/non-CNS) | Permanently discontinue |
| Venous thrombosis | 3 | Hold temporarily |
| | 4 | Permanently discontinue |
| Arterial thrombosis | Any Grade | Permanently discontinue |
| Congestive Heart Failure | ≥ 3 | Permanently discontinue |
| Proteinuria | 2-3 | - For 2+ dipstick: may administer bev, obtain 24-hour urine sample prior to next bev dose Suspend bev for ≥2 g /24 hours and resume when proteinuria is <2 g /24 hours and protein creatinine ratio <2.0 - For 3+ dipstick: obtain 24 hour urine sample prior to bev administration Suspend bev for ≥2 g /24 hours and resume when proteinuria is <2 g /24 hours and protein creatinine ratio <2.0 |
| | 4 | Permanently discontinue |
| GI perforation | Any grade | Permanently discontinue |
| PRES/RPLS | Any grade | Permanently discontinue |
| Fistula | Any grade TE fistula | Permanently discontinue |
| | ≥3 (other than TE) | Permanently discontinue |
| Febrile neutropenia/ thrombocytopenia | 4 | Hold temporarily |
| Other unspecified bev-related AE | 3 | Hold until recovery to ≤ Grade 1 |
| | 4 | Permanently discontinue |

Gastrointestinal Perforation

Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

Fistula

Bevacizumab should be permanently discontinued in patients who develop any grade tracheoesophageal and temporarily hold or permanently discontinued in the case of grade ≥ 2 fistula in any other site.

Surgical Procedures/Wound Healing Complications

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.

Bevacizumab therapy should be withheld 60 days before elective surgery. CVAD placement and complications will be monitored as an assessment of treatment-related complications. Date of placement of CVAD will be noted in the medical record and recorded in the eCRF. Episodes of CVAD removal or replacement will be recorded. Episodes of CVAD-related thrombosis, infection, or dysfunction will be recorded.

Necrotising fasciitis including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension

Patients should be monitored for the development or worsening of hypertension via frequent blood pressure measurement. Blood pressure measurements should be taken after the patient has been in a resting position for ≥ 5 minutes. Repeat

measurements of blood pressure for verification should be undertaken if the initial reading is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic blood pressure.

- Grade 1 hypertension: Asymptomatic, transient (< 24 hrs) increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits. Intervention not indicated.
- Grade 2 hypertension: Recurrent or persistent (> 24 hr) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits. Monotherapy with ACE-inhibitor may be indicated. Once controlled to < 150/100 mmHg, patients may continue bevacizumab therapy.
- Grade 3 hypertension: Requiring more than one anti-hypertensive or more intensive therapy than previously. Addition of diuretic to ACE-inhibitor may be indicated; if hypertension is not controlled a third anti-hypertensive drug (calcium channel blocker) should be added.

Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled with triple-drug medication.

Proteinuria

All patients will have a dipstick urinalysis or 24 hour protein determination performed within 48 hours prior to the first bevacizumab dose and thereafter every 8 weeks. Adjustment of bevacizumab administration for proteinuria of ≥ 2 g/24h will occur according to the following guidelines, listed below:

- < 2+ (dipstick): no additional evaluation is required.
- $\geq 2+$ (dipstick): Collect 24-hour urine to determine the total protein within 3 days prior to the next scheduled dose:
 - 24-hour proteinuria ≤ 2 g: Administer bevacizumab as scheduled.
 - 24-hour proteinuria > 2 g: Bevacizumab treatment should be withheld pending next 24 hour total protein.

Repeat 24-hour urine protein ≤ 2 g: Administer bevacizumab as schedule. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24h.

Repeat 24-hour urine protein > 2 g: Bevacizumab dose should be withheld until 24-hour protein has decreased to ≤ 2 g. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to ≤ 1 g/24 h.

Nephrotic syndrome (Grade 4, CTCAEv4.0): Discontinue bevacizumab treatment.

Thrombosis/Embolism

All toxicity will be graded according to CTCAEv4.0 guidelines. For patients who develop thrombosis/embolism the following action is recommended:

Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events of any grade and in patients to develop grade 3 venous thrombosis

Congestive heart failure

Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with bevacizumab, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy.

Events consistent with congestive heart failure were reported in clinical trials with symptoms ranging from asymptomatic declines in left ventricular ejection fraction to symptomatic congestive heart failure, requiring treatment or hospitalisation. Patients developing \geq G3 congestive heart failure should permanently discontinue bevacizumab treatment.

Haemorrhage

Patients who develop grade ≥ 2 pulmonary or CNS (any grade) or grade ≥ 3 hemorrhage should discontinue bevacizumab treatment.

Patients who develop grade 3 non-pulmonary and non – CNS hemorrhage should hold bevacizumab until all of the following criteria are met:

- The bleeding has resolved and haemoglobin is stable.

- There is no bleeding diathesis that would increase the risk of therapy.
- There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.

Posterior Reversible Encephalopathy Syndrome (PRES/RPLS)

Bevacizumab should be permanently discontinued in patients who develop any grade PRES/RPLS

8.2. Concomitant medications and management of specific adverse events

Acute cholinergic syndrome

Atropine sulfate can be used, at the discretion of the investigator, as secondary prophylaxis or therapy of early onset cholinergic syndrome induced by irinotecan. Secondary prophylactic or therapeutic administration of 0.25-1 mg of subcutaneous atropine can be considered (unless clinically contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after infusion of irinotecan).

Antiemetic prophylaxis

To be chosen on the basis of the chemotherapy regimen according to the center's guidelines.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be ameliorated by administration of atropine (0.25 mg SC). Atropine should not be given prophylactically during cycle 1.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be lifethreatening. Patients and patients' caregivers should be carefully informed of possible severe toxic effects such as diarrhea and abdominal cramps. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of irinotecan) at the first episode of poorly formed or loose stools or the earliest onset of

bowel movements more frequent than normally expected for the patient. The patient should also be instructed to notify the Investigator if diarrhea or abdominal cramps occur. If diarrhea persists for more than 24 hours despite loperamide, the patient should be instructed to take a fluoroquinolone antibiotic and to re- contact the treating Investigator. The patient should be hospitalised for parenteral support and loperamide should be replaced by another anti-diarrheal treatment (e.g. octreotide). Patients should have a supply of fluoroquinolone antibiotic available at home. The recommended dosage regimen for loperamide previously used in irinotecan clinical trials consists of the following: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended. If diarrhea occurs it is of vital importance that measures are taken to avoid dehydration and electrolyte imbalance. Patients should be supported as clinically indicated. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their Investigator to discuss any laxative use. Abdominal cramps should be treated the same as for diarrhea.

Extravasation

No severe extravasation reactions have been observed so far with CPT-11 and Oxaliplatin. As a general recommendation, in the event of extravasation, the following advice should be observed (like for any drug):

1. stop the infusion immediately,
2. do not remove the needle or cannula,
3. aspirate as much infiltrated drug as possible from the subcutaneous site with the same needle,
4. apply ice to the area for 15 to 20 minutes every 4 to 6 hours for the first 72 hours,
5. watch the area closely during the following days in order to determine whether any further treatment is necessary.

Hematopoietic growth factors

G-CSF is not recommended as primary prophylaxis, but it can be used in secondary prophylaxis in case of:

- Precedent febrile neutropenia;
- Precedent grade 4 neutropenia lasting 5 days or more;
- More than 2 delays of the planned therapy due to neutropenia.

Prohibited treatment

High dose aspirin (>325 mg/day) and anticoagulants for therapeutic purpose are not allowed in combination with Bevacizumab.

9. STATISTICAL METHODS

This is a prospective, open-label, multicentric, randomized phase III study in which patients, stratified according to center, ECOG PS (0 vs 1, 2), primary tumor location (right vs left or rectum) and previous adjuvant chemotherapy, will be randomized to receive one of two treatment strategies, as specified in the Paragraph “Study design”.

9.1. Primary endpoint

The primary endpoint is Progression Free Survival 2 (PFS2).

PFS2 will be defined as beginning with randomization and ending with the first of the following events: a) death; b) disease progression on any treatment given after 1st progression. For patients that will not receive any treatment within 3 months after 1st progression, PFS2 will be equal to PFS. The determination of disease progression will be based on investigator-reported measurements. Disease status will be evaluated according to RECIST 1.1 criteria.

Censoring rules for PFS2 will be: end of study without PD, loss at follow-up. Curative surgery for metastasis will not result in censoring for PFS2.

PFS2 will be analyzed both in the intention-to-treat population (primary analysis) and in the per-protocol population.

9.2. Secondary endpoints

Secondary endpoints of this study are the following:

Progression free survival (PFS) is defined as the time from randomization to the first documentation of objective disease progression or death due to any cause, whichever occurs first. PFS will be censored on the date of the last evaluable on study tumor assessment documenting absence of progressive disease for patients who are alive, on study and progression free at the time of the analysis. Alive patients having no tumor assessments after baseline will have time to event censored on the date of randomization.

2nd-Progression free survival (2nd-PFS) is defined as the time from the beginning of the second-line treatment to the documentation of objective disease progression or death due to any cause, whichever occurs first. 2nd-PFS will be censored on the date of the last evaluable on study tumor assessment documenting absence of progressive disease for patients who are alive, on study and 2nd-progression free at the time of the analysis. 2nd-PFS will be analyzed both in the intention-to-treat population (whichever 2nd-line treatment will be adopted) and in the per-protocol population.

Time to failure of strategy (TFS) is defined as the time time from randomization to the first of the following events: death; patient requires the addition of a new therapeutic agent (i.e. an agent not included in the original strategy); patient experiences disease progression while being treated with all agents that are components of the initial treatment strategy (except for agents which cannot be used because of persistent toxicity or contraindications); or patient experiences disease progression during a partial or complete treatment holiday from initial treatment strategy and receives no further therapy within 3 months. Subjects who did not have an event as stated above while on study will be censored at the last evaluable radiographic assessment date. TFS will be analyzed both in the intention-to-treat population (primary analysis) and in the per-protocol population.

Overall survival (OS) is defined as the time from randomization to the date of death due to any cause. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive.

Objective Response Rate is defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria, during the induction and the maintenance phases of treatment. The determination of clinical response will be based on investigator reported measurements. Responses will be evaluated every 8 weeks.

Early Objective Response Rate is defined as the percentage of patients, relative to the total of the enrolled subjects, achieving a $\geq 20\%$ decrease in the sum of diameters of RECIST target lesions at week 8 compared to baseline.

R0 Resection Rate is defined as the percentage of patients, relative to the total of enrolled subjects, undergoing secondary R0 resection of metastases. Secondary R0 surgery is defined as microscopically margin free complete surgical removal of all residual disease, performed during treatment or after its completion, allowed by tumoral shrinkage and/or disappearance of one or more lesions.

Overall Toxicity Rate is defined as the percentage of patients, relative to the total of enrolled subjects, experiencing any adverse event, according to National Cancer Institute Common Toxicity Criteria (version 4.0), during the induction and the maintenance phases of treatment.

Toxicity Rate is defined as the percentage of patients, relative to the total of enrolled subjects, experiencing a specific adverse event of grade 3/4, according to National Cancer Institute Common Toxicity Criteria (version 4.0), during the induction and the maintenance phases of treatment.

9.3. Study populations for primary and secondary analyses

Intention to treat population (ITT)

The ITT population will include all randomized patients. The ITT population will be the population for evaluating all primary and secondary endpoints, with the exception of toxicity rate and overall toxicity rate.

Safety population (SP)

The SP will include all patients who receive at least one dose of the study medication designated according to the randomization arm. The SP will be the population for evaluating treatment administration/compliance and safety.

Per-protocol population

The per-protocol population will include patients that proceeded according to the protocol, receiving at least one cycle of FOLFOX plus bev as first-line treatment and at least one cycle of FOLFIRI plus bev as second-line treatment (arm A) and at least one cycle of FOLFOXIRI plus bev as first-line treatment and at least one cycle of 5-FU +/- oxaliplatin +/- irinotecan plus bev as second-line treatment (arm B).

9.4. Analysis of endpoints

Analysis of primary endpoint

The primary analysis of PFS2 will be performed in the ITT population. An unstratified log rank test will be used to compare PFS2 time between the two treatment arms with a two-sided alpha level equal to 0.0131 and 0.0455 at the interim and/or final analyses, respectively. Hazard ratios and 95 percent confidence intervals will be calculated with the use of the Cox proportional-hazards model. Survival curves will be calculated according to Kaplan–Meier method. A log-rank test stratified by means of the same factors as used for randomization will also be performed, as well as a multivariable model including all the baseline variables that will result significantly ($p < 0.05$) related to PFS2 at the univariate analyses.

Analysis of secondary endpoints

A two-sided log-rank test will be used to compare study arms in terms of PFS, TFS and OS. Hazard ratios and 95 percent confidence intervals will be calculated with the use of the Cox proportional-hazards model. Survival curves will be calculated according to Kaplan–Meier methods. Log-rank tests stratified by the same factors as

used for randomization will also be performed, as well as multivariable models including all the significant baseline variables.

Best overall response rate will be calculated as the number of patients with a CR or PR as best response divided by the total number of enrolled patients. The corresponding exact 2-sided 95% confidence interval will be calculated using a method based on the binomial distribution.

R0 resection rate will be calculated as the number of patients undergoing secondary R0 resection of metastases divided by the total number of randomized patients in each arm. The corresponding exact 2-sided 95% confidence interval will be calculated using a method based on the binomial distribution.

Toxicity rates and overall toxicity rate will be calculated as the number of patients experiencing a specific adverse event of grade 3/4 or any adverse event of grade 3/4 divided by the total number of randomized patients and it will be summarized by the two arms of treatment and also by each study medication/type of treatment and by periods (before first PD and after first PD). Also a separate summary of AE grade 3/4 will be provided for patients undergoing secondary R0 resection of metastases. The corresponding exact 2-sided 95% confidence interval will be calculated using a method based on the binomial distribution.

9.5. Sample size

Based on the assumption that PFS2 of each arm follows an exponential distribution and the true hazard ratio (HR) for PFS2 is 0.77 between experimental group (arm B) vs. control group (arm A), 466 events are required for a two-sided unstratified log-rank test with $\alpha = 0.05$ to have 80% power. Assuming a proportion of PFS2 equal to 50% at 15 months in arm A, this treatment effect can be translated to a 9% absolute improvement in PFS2 at 15 months in arm B. Assuming an accrual rate of 200 subjects/year, a minimum follow up period equal to 1.5 years and an overall dropout

rate equal to 5%, it is estimated that the enrollment of 654 subjects, randomized in a 1:1 ratio, is required.

We plan a group sequential design with 1 interim analysis to assess the primary efficacy endpoint. The analyses will take place at 2/3 (303 events) of the primary events using an O'Brien Fleming alpha-spending rule. The interim analysis will assess superiority of experimental arm to control group for the primary endpoint because the study will only be considered for early termination if superiority is met. The first interim analysis will have a two sided alpha level of 0.0131. According to the O'Brien Fleming spending rule this will leave a two sided alpha level of 0.0455 for the final analysis. The total type I error rate will be only slightly increased.

10. ETHICAL ISSUES

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRB(s) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (eg, IEC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the Sponsor or the investigator without agreement by both parties. However, the investigator or the Sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IEC/IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/Sponsor. Any deviations from the protocol must be explained and documented by the investigator.

10.1. Informed Consent

The investigator must explain to each patient (or legally authorised representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical treatment or relationship with physician. The informed consent will be given by means of standard written statement, written in non-technical language. The patient should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the document, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign documents. No patient can enter the study before her informed consent has been obtained. The informed consent is part of the protocol and must be submitted by the investigator with to the local ethical committee.

A copy of the patient's signed written consent will be kept by the center in the proper section of the Investigator Site File.

10.2. Patient protection

The names of patients will not be recorded; a sequential identification number will be attributed to each patient registered in the trial. This number will identify the patient and must be included on all electronic Case Report Forms.

In order to avoid identification errors, patients initials (maximum of 2 letters) and date of birth will also be reported on the Case Report Forms.

Investigators will guarantee that all persons involved in this study will respect the confidentiality of any information concerning the trial subject.

All parties involved in this clinical trial will maintain the strict confidentiality to assure that neither the person nor the family privacy of the patient participating in

the trial is violated; appropriate measures shall be taken to avoid the access of non authorized persons to the trial data. The processing of the personal data of patients taking part in the trial, and in particular regarding data concerning consent, shall comply with local law on the privacy (Legge delega 127/2001) and with the European Directive on the Privacy of data (95/46/EC).

The patient can withdraw consent whenever he wants and further data will not be collected, even if the already collected data will be used for the study's analyses.

10.3. Confidential subject information for samples storage

For the storage of biological samples, specific means will be taken to ensure the subject's right to privacy and the pertinent guidance documents and regulations will be considered.

Subjects may withdraw their consent to store the biological samples. If the patient withdraws his consent from the study within 5 years, the biological samples will be destroyed. After 5 years, biological samples will be anonymized completely. At that time the samples cannot be identified in any way. The samples will be maintained for potential analysis for 15 years from the acquisition. Samples will be destroyed according to GONO policies and procedures.

Samples will be collected and sent to the laboratory designated for the trial where they will be processed.

Tumor tissue samples, blood and plasma samples will be stored at Oncologia Medica 2 Universitaria of Azienda Ospedaliero-Universitaria Pisana – Translational Research and New Technologies Department– University of Pisa, under the responsibility of Dr. Loupakis.

To maintain privacy of information collected from samples obtained for storage and future analysis, GONO has developed secure policies and procedures to maintain subject privacy. At the clinical site, a unique Code will be placed on the blood sample

for transfer to the storage facility. The Code is a random number used only to identify the biosample of each subject. No other personal identifiers will appear on the sample tube. The first Code will be replaced with a Sample Code at the Central Laboratory or at the GONO designated facility. This sample is now a single coded sample. The Sample Code is stored separately from all previous sample identifiers. A secure code, hereinafter referred to as a “first coding key”, will be utilized to match the Sample Code to the original blood code and subject number to allow clinical information collected during the course of the trial to be associated with the biosample. This “first coding key” will be transferred by the central laboratory or GONO designated facility under secure procedures to the GONO designated as the entrusted keyholder to maintain confidentiality of the biosamples. The Sample Code will be logged into the primary biorepository database, and in this database this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The sample will be stored in a designated repository site with secure policies and procedures for sample storage and usage.

10.4. Ethics Committe (EC)

The Investigator must submit this protocol to the local Ethics Committee and is required to forward a copy of the written approval to the CRP.

The EC approval must report, the identification of the trial (title, protocol number and version), the documents evaluated (protocol, informed consent material, advertisement when applicable) and the date of their version.

10.5. Administrative responsibilities

The Coordinating Center (U.O. Oncologia 2 Universitaria – Polo Oncologico Azienda Ospedaliero-Universitaria Pisana, AOUP) and the Data Center (Centro Coordinamento Sperimentazioni Cliniche of Istituto Toscano Tumori – Azienda Ospedaliero-Universitaria Careggi) will be responsible for:

- reviewing the protocol
- centralizing databases
- centralizing data validation according to Data Validation Plan
- controlling the quality of the reported data
- emitting Data Query Forms
- generating study program reports
- generating the Statistical Analysis Plan
- perform statistical analysis

10.6. Trial sponsorship and financing

- The present study is an investigator-initiated trial, carried out by participating clinicians, who have the intellectual ownership of the results.
- The study is sponsored by Gruppo Oncologico Nord-Ovest (G.O.N.O.) Cooperative Group Via G. Mameli, 3 – Genoa (ITALY), who will provide the economical support for costs related to data management, statistical analysis and the other activities of central and group coordinating centers.
- Roche SpA will provide vials of Bevacizumab beyond progression in both arms and partial financial support for study costs.
- No funds can be provided to ethical committees and single participating centers.
- The study will be conducted according to the current regulations.

11. STUDY MONITORING

11.1. Quality assurance

Each participating Investigator will be responsible for ensuring data quality as planned in the Data Validation Plan document. Each reported information will be systematically checked for consistency, completeness and accuracy by the Coordinating Data Center that will issue Data Query Forms in case of inconsistent data. Local quality control will be provided by coordinating centers of each participating group, which will be responsible of monitoring the centers belonging to their group.

11.2. Responsibilities of the investigators

The Investigators undertake to perform the study in accordance with ICH Good Clinical Practice and Good Clinical Practice for Trials on Medicinal Products in the European Community (ISBN 92 - 825-9563-3).

The Investigator is required to ensure his compliance to the procedures required by the protocol with respect to the investigational drug schedule and visit schedule. The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to the instructions provided.

The Investigator has responsibilities to the Health Authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms. The main duty of the Trial Monitor is to help the Investigator and the Coordinators to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, to review the study progress, the investigators and subjects adherence to protocol requirements.

During each monitoring visits, the following points will be scrutinized:

- subject informed consent
- subject recruitment and follow-up

- study drug allocation
- subject compliance to the study treatment
- study treatment accountability
- Adverse Event documentation and reporting

11.3. Source documents requirements

According to the guidelines on ICH Good Clinical Practice, the monitor of the study will check the case report form entries against the source documents. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

Considering the primary end point of the study, independent review of objective response will be performed by an external panel. For this reason, a copy (either on CD or radiological film) of each CT or RMN scan performed during the study will be required.

11.4. Use and completion of electronic case report forms (e-CRFs)

It is the responsibility of the Investigator to prepare and maintain adequate and accurate e-CRFs for each patient enrolled in the study. All e-CRFs should be completed to ensure accurate interpretation of data.

12. ADVERSE EVENTS

12.1. Definition of adverse event

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2). See below (specific table), for guidelines to drug-event relationship assessment.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Patients will be instructed by the Investigator to report the occurrence of any adverse event.

Assessment of drug-event relationship

| Relationship | Description |
|-------------------------|---|
| <i>unrelated</i> | There is no evidence of any causal relationship |
| <i>unlikely</i> | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatments). |
| <i>possible</i> | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event |

| | |
|------------------------------|--|
| | (e.g. the patient's clinical condition, other concomitant treatments). |
| <i>probable</i> | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| <i>definitely</i> | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |
| <i>not assessable</i> | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

12.2. Definition of Adverse Drug Reactions (ADR)

All untoward and unintended responses to a medicinal product related to any dose administered.

The phrase “responses to a medicinal product” means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

A serious ADR (SADR) is an ADR that meets the definition of serious (provided below).

12.3. Definition of Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that:

- is fatal
- is life threatening (places the subject at immediate risk of death):
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care

facility. Any adverse event that does not meet one of the definitions of serious (i.e., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for the performing of protocol-required procedures or administration of study treatment is not classified as an SAE.

All adverse events which do not meet any of the criteria for serious should be regarded as non-serious adverse events.

All serious adverse events occurring during the study treatment period must be reported within 24 hours according to the procedure described below. Any late SAE (occurring after this 30 days period) possibly or probably related to the study treatment should follow the same reporting procedure.

Progression of colorectal cancer leading to one of the above should not be reported as a serious adverse event.

12.4 ADVERSE EVENTS OF SPECIAL INTEREST (AESI) to bevacizumab

Non-serious and serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) Adverse events of special interest for this study include the following:

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3

- PRES (or RPLS; any grade)
- CHF \geq grade 3
- Non-GI fistula or abscess \geq grade 2

Other Non-Serious or Serious AESIs for this study include the following:

a. *Cases of potential drug-induced liver injury* that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law. The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin);
- treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice.

The most appropriate diagnosis or, (if a diagnosis cannot be established) the abnormal laboratory values, should be recorded on the Adverse Event eCRF page and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest.

b. *Suspected transmission of an infectious agent by the study drug*, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose (including partial dose) of study treatment until 6 months after the last study treatment. AESIs will be followed until resolution. All these AESIs must be reported to the Sponsor immediately (i.e. no more than 24 hours after learning of the event).

12.5. Deaths reporting procedure

Any death occurring between the *randomization* and 30 days following the *treatment* must be reported to the Sponsor within 24 hours, regardless of the relation to study drug(s). Deaths occurring later than 30 days after the treatment should be reported on the death report form section of the e-CRF regardless of cause.

12.6. Pregnancies reporting procedure

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

12.7. Reporting procedure

a. Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; outcome, assessment of relatedness to study treatment; and action taken.

Medically significant adverse events considered related to the treatment by the investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

b. Serious Adverse Events Reporting Procedures

Serious adverse events will be collected and recorded throughout the study period, defined as through to 6 months after the last dose of the treatment or the end of the study (including the follow-up period), whichever is longer.

The investigator should notify the Sponsor of all serious adverse events occurring at the site(s) in accordance with local procedures, statutes and the European Clinical Trial Directive (where applicable). The Sponsor will medically review all SAEs.

The Sponsor will ensure the notification of the appropriate Ethics Committees, Competent Authorities and participating Investigators of all serious adverse events occurring at the site(s) in accordance with local legal requirements, statutes and the European Clinical Trial Directive.

12.8. Follow-up

Patients withdrawn from the study treatment due to any adverse event will be followed at least until the outcome is determined, even if it implies that the follow-up

continues after the patients has left the trial, and where appropriate until the end of the planned period of follow-up.

In case of serious adverse event, the patient must be followed until clinical recovery is complete and laboratory results have returned to normal, or until symptoms have stabilized. This may imply that the follow-up will continue after the patient has left the trial.

Further information will be noted on the SAE form, by ticking the box marked "follow-up" and will be sent to the Coordinating Center as information becomes available.

12.9 Post-study follow up

After study drug treatment ends, anti-cancer medications taken by the patient should be documented in the eCRF.

Patients will be evaluated approximately every month to determine their survival status. Telephone follow-up is acceptable. Site staff must use caution when contacting the patient's family for this information, especially if they are no longer under the care of the investigator, so as to not inadvertently cause any distress to the family of a patient who is no longer alive.

During this period, If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial, the investigator shall, without undue delay, report the serious adverse event to the Sponsor.

The investigator should report these events directly to the Sponsor, by completing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form that will be sent to the Coordinating Center.

Subjects who withdraw consent from study drug treatment should enter the post-study follow-up period (unless consent to follow-up is specifically withdrawn).

Details should be documented on the specified Serious Adverse Event Form.

**Please fax the report to 050.992069
and mail a .pdf scan version to:
tribe2study@gmail.com**

The Sponsor will also send the report to national authorities, Ethic Committees (EC) and investigators as appropriate, according to local regulations.

In addition, the Sponsor shall supply Roche with a copy of all above mentioned safety report regardless of the causality assessment concerning the Pharmaceutical Product administration.

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14. APPENDICES

14.1. Study Synopsis (English Version)

Title

First-line FOLFOXIRI plus bevacizumab followed by reintroduction of FOLFOXIRI plus bevacizumab at progression versus FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab at progression in first- and second line treatment of unresectable metastatic colorectal cancer patients

Version

2.1 – 2nd September 2014

Sponsor

Gruppo Oncologico Nord-Ovest G.O.N.O.

Coordinating Investigator

Prof. Alfredo Falcone

U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana
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Phase of study

Phase III

Indication

Metastatic colorectal cancer (mCRC)

Study Rationale

- The association of chemotherapy and bevacizumab (bev) is a standard option for the first-line treatment of unresectable metastatic colorectal cancer patients. In particular, an oxaliplatin-based doublet plus Bev is a widely used regimen in this setting.
- Recent results from phase III TRIBE trial demonstrated that the triplet FOLFOXIRI plus bev, compared to first-line FOLFIRI plus bev, provides a significant advantage in terms of PFS and RR and a benefit in terms of OS with a trend towards significance. At the same time, phase II OLIVIA trial showed that FOLFOXIRI plus bev allows to achieve an higher R0 resection rate, with encouraging results in terms of PFS, in the setting of unresectable mCRC patients with liver-limited disease.
- A sustained inhibition of angiogenesis across different lines of treatment is an efficacious strategy in the management of mCRC. As demonstrated by both ML18147 and BEBYP trials, the prosecution of bev beyond the clinical evidence of disease progression provides a survival benefit.
- The optimal duration of chemotherapy plus bev is highly debated. Phase III OPTIMOX1, 2, COIN, CONcePT and GISCAD trials address this issue, substantially evidencing that the choice not to continuously administer the treatment until the evidence of disease progression, but to alternate periods of less intensive chemotherapy or chemo-holidays can be pursued without compromising patients' prognosis.
- Both phase III randomized SAKK 41/06 and CAIRO-3 trials addressed the issue of maintenance with bev. SAKK 41/06 did not demonstrate the non-inferiority of interrupting instead of prosecuting bev until the time of progression. CAIRO-3 trial met its primary endpoint PFS2 evidencing an advantage by the prosecution of Capecitabine plus Bev until disease progression, compared to observation.
- The opportunity to alternate induction periods, able to rapidly induce a relevant tumor shrinkage, and maintenance phases in the disease history of mCRC patients could be considered a valuable strategy.

On the basis of these considerations, a first-line doublet plus bev followed by a second-line switched doublet (from oxaliplatin to irinotecan and viceversa) plus bev is a standard option for mCRC patients. Only retrospectively collected data are currently available about the efficacy of first-line FOLFOXIRI plus bev followed by second-line rechallenge with FOLFOXIRI plus bev. We therefore designed the present phase III randomized trial of first-line FOLFOXIRI plus bev followed by reintroduction of FOLFOXIRI plus bev at progression versus FOLFOX plus bev followed by FOLFIRI plus bev at progression in first- and second-line treatment of unresectable mCRC patients.

Primary objective

To compare the two proposed strategies in terms of Progression Free Survival 2 (PFS2)

Secondary objectives

To compare the two proposed strategies in terms of :

- 1st-line Progression-free survival (PFS)
- 2nd-line Progression-free survival (2nd-PFS)
- Time to failure of strategy (TFS)
- Overall Survival (OS)
- Response rate in 1st and 2nd-line
- Early Objective Response
- R0 Resection Rate
- Safety profile
- Translational analyses.

Definition of primary endpoint

PFS2 will be defined as beginning with randomization and ending with the first of the following events: a) death; b) disease progression on any treatment given after 1st progression. For patients that will not receive any treatment within 3 months after 1st progression, PFS2 will be equal to PFS. Censoring rules for PFS2 will be: end of study without PD, loss at follow-up. Curative surgery for metastases will not result in censoring for PFS2

Definition of secondary endpoints

PFS is defined as the time from randomization to the first documentation of objective disease progression or death due to any cause, whichever occurs first. The determination of disease progression will be based on investigator-reported measurements. Disease status will be evaluated according to RECIST 1.1 criteria.

2nd PFS is defined as the time from the beginning of the second-line treatment to the documentation of objective disease progression or death due to any cause, whichever occurs first. The determination of disease progression will be based on investigator-reported measurements. Disease status will be evaluated according to RECIST 1.1 criteria. 2nd-PFS will be analyzed both in the intention-to-treat population (whichever 2nd-line treatment will be adopted) and in the per-protocol population.

TFS is defined as the time from randomization to the first of the following events: death; patient requires the addition of a new therapeutic agent (i.e. an agent not included in the original strategy); patient experiences disease progression while being treated with all agents that are components of the initial treatment strategy (except for agents which cannot be used because of persistent toxicity or contraindications); or patient experiences disease progression during a partial or complete treatment holiday from initial treatment strategy and receives no further therapy within 3 months. Subjects who did not have an event as stated above while on study will be censored at the last evaluable radiographic assessment date.

OS is defined as the time from randomization to the date of death due to any cause.

Objective response rate is defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria.

R0 resection rate is defined as the percentage of patients, relative to the total of enrolled subjects, undergoing secondary R0 resection of metastases.

Overall toxicity rate is defined as the percentage of patients, relative to the total of enrolled subjects, experiencing any adverse event, according to National Cancer Institute Common Toxicity Criteria (version 4.0), during the induction and the maintenance phases of treatment.

Statistical considerations

Based on the assumption that PFS2 of each arm follows an exponential distribution and the true hazard ratio (HR) for PFS2 is 0.77 between experimental group (arm B) vs. control group (arm A), 466 events are required for a two-sided unstratified log-rank test with $\alpha = 0.05$ to have 80% power.

Assuming a proportion of PFS2 equal to 50% at 15 months in arm A, this treatment effect can be translated to a 9% absolute improvement in PFS2 at 15 months in arm B.

Assuming an accrual rate of 200 subjects/year, a minimum follow up period equal to 1.5 years and an overall dropout rate equal to 5%, it is estimated that the enrollment of 654 subjects, randomized in a 1:1 ratio, is required.

The primary analyses of PFS2 will be performed in the ITT population. An unstratified log rank test will be used to compare PFS2 time between the two treatment arms with a two alpha level equal to 0.0131 and 0.0455 at the interim and/or final analyses, respectively.

We plan a group sequential design with 1 interim analysis to assess the primary efficacy endpoint. The analyses will take place at 2/3 (303 events) of the primary events using an O'Brien Fleming alpha-spending rule. The interim analysis will assess superiority of experimental arm to control group for the primary endpoint because the study will only be considered for early termination if superiority is met. The first interim analysis will have a two sided alpha level of 0.0131. According to the O'Brien Fleming spending rule this will leave a two sided alpha level of 0.0455 for the final analysis. The total type I error rate will be only slightly increased.

Inclusion Criteria

- Histologically proven diagnosis of colorectal cancer
- Initially unresectable metastatic colorectal cancer not previously treated with chemotherapy for metastatic disease
- At least one measurable lesion according to RECIST1.1 criteria
- Availability of a tumoral sample
- Male or female of 18-75 years of age
- ECOG PS \leq 2 if aged $<$ 71 years, ECOG PS = 0 if aged 71-75 years
- Life expectancy of at least 12 weeks
- Previous adjuvant chemotherapy allowed only if with fluoropyrimidine monotherapy and more than 6 months elapsed between the end of adjuvant and first relapse
- Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hgb >9 g/dl
- Total bilirubin 1.5 time the upper-normal limits (UNL) of the normal values and ASAT (SGOT) and/or ALAT (SGPT) $<2.5 \times$ UNL (or $<5 \times$ UNL in case of liver metastases) alkaline phosphatase $<2.5 \times$ UNL (or $<5 \times$ UNL in case of liver metastases)
- Creatinine clearance >50 mL/min or serum creatinine $1.5 \times$ UNL
- Urine dipstick of proteinuria $<2+$. Patients discovered to have $2+$ proteinuria on dipstick urinalysis at baseline, should undergo a 24-hour urine collection and must demonstrate <1 g of protein/24 hr
- Women of childbearing potential must have a negative blood pregnancy test at the baseline visit. For this trial, women of childbearing potential are defined as all women after puberty, unless they are postmenopausal for at least 12 months, are surgically sterile, or are sexually inactive.
- Subjects and their partners must be willing to avoid pregnancy during the trial and until 6 months after the last trial treatment. Male subjects with female partners of childbearing potential and female subjects of childbearing potential must, therefore, be willing to use adequate contraception as approved by the investigator (barriere contraceptive measure or oral contraception)
- Will and ability to comply with the protocol
- Written informed consent to study procedures and to molecular analyses

Exclusion criteria

- Radiotherapy to any site within 4 weeks before the study
- Previous adjuvant oxaliplatin-containing chemotherapy
- Previous treatment with bevacizumab
- Untreated brain metastases or spinal cord compression or primary brain tumours
- History or evidence upon physical examination of CNS disease unless adequately treated
- Symptomatic peripheral neuropathy > 2 grade NCIC-CTG criteria
- Serious, non-healing wound, ulcer, or bone fracture
- Evidence of bleeding diathesis or coagulopathy
- Uncontrolled hypertension and prior history of hypertensive crisis or hypertensive encephalopathy
- Clinically significant (i.e. active) cardiovascular disease for example cerebrovascular accidents (≤ 6 months), myocardial infarction (≤ 6 months), unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication
- Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of study enrolment
- Any previous venous thromboembolism > NCI CTCAE Grade 3
- History of abdominal fistula, GI perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to the first study treatment.
- Current or recent (within 10 days prior to study treatment start) ongoing treatment with anticoagulants for therapeutic purposes
- Chronic, daily treatment with high-dose aspirin (> 325 mg/day)
- Treatment with any investigational drug within 30 days prior to enrollment or 2 investigational agent half-lives (whichever is longer)
- Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of localized basal and squamous cell carcinoma or cervical cancer in situ
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study
- Lack of physical integrity of the upper gastrointestinal tract, malabsorption syndrome, or inability to take oral medication
- Pregnant or lactating women. Women of childbearing potential with either a positive or no pregnancy test at baseline. Sexually active males and females (of childbearing potential) unwilling to practice contraception during the study (barriere contraceptive measure or oral contraception).

Study treatment

Arm A - mFOLFOX-6 plus bev (to be repeated every 2 weeks for a maximum of 8 cycles)

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Oxaliplatin 85 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluoruracil 400 mg/sqm iv bolus, day 1
- 5-fluoruracil 2400 mg/sqm 48 h-continuous infusion, starting on day 1

If no progression occurs, patients will receive maintenance **5-FU/LV plus bev** at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal. The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluoruracil because of adverse events, patient's refusal or investigator's choice. At the time of disease progression patients will receive **FOLFIRI plus bev*** (to be repeated every 2 weeks for a maximum of 8 cycles):

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Irinotecan 180 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluoruracil 400 mg/sqm iv bolus, day 1
- 5-fluoruracil 2400 mg/sqm 48 h-continuous infusion, starting on day 1

*Doses may be modified according to patient's tolerance to 1st-line regimen.

If no progression occurs, patients will receive maintenance **5-FU/LV plus bev** at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal. The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluoruracil because of adverse events, patient's refusal or investigator's choice.

Arm B - FOLFOXIRI plus bev (to be repeated every 2 weeks for a maximum of 8 cycles):

- Bevacizumab 5 mg/kg iv over 30 minutes, day 1
- Irinotecan 165 mg/sqm iv over 60 minutes, day 1
- Oxaliplatin 85 mg/sqm iv over 2 hours, day 1
- L-Leucovorin 200 mg/sqm iv over 2 hours, day 1
- 5-fluorouracil 3200 mg/sqm 48 h-continuous infusion, starting on day 1

If no progression occurs during FOLFOXIRI plus bev, patients will receive maintenance 5-FU/LV plus bev at the same dose used at the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal. The prosecution of bev until disease progression is recommended also if 5-fluorouracil is interrupted because of adverse events, patient's refusal or investigator's choice. At the time of disease progression, patients will re-introduce FOLFOXIRI plus bev at the same doses and schedule previously tolerated, for a maximum of 8 cycles. If persistent neurotoxicity \geq G2, FOLFIRI plus bev will administered for a maximum of 8 cycles. If no progression occurs during FOLFOXIRI plus bev, patients will receive maintenance 5-FU/LV plus bev at the same dose used in the last cycle of the induction treatment. 5-FU/LV plus bev will be repeated biweekly until disease progression, unacceptable toxicity or patient's refusal. The prosecution of bev until disease progression is recommended also in the case of interruption of 5-fluorouracil because of adverse events, patient's refusal or investigator's choice.

Study Design Diagram

Arm A: → → ↙



OR ↙

Arm B: ↙



Study procedures overview

| Procedure | Screening (within 28 days before random) | Baseline | Before every cycle ¹ | Every 8 wks ¹ | After the 2nd evidence of PD |
|---|--|----------|---------------------------------|--------------------------|------------------------------|
| <i>Informed Consent</i> | X | | | | |
| <i>Complete medical history</i> | X | | | | |
| <i>Inclusion/Exclusion Criteria Checked</i> | X | | | | |
| <i>Tumor assessment (total-body CT or abdomen MRI + chest CT)</i> | X | | | X | |
| <i>Collection of a CD-ROM copy of CT scan</i> | X | | | X | |
| <i>12-lead ECG</i> | X | | | | |
| <i>ECOG PS</i> | X | X | X | X | |
| <i>Physical examination</i> | X | | X | X | |
| <i>Complete blood examination²</i> | X | | | X | |
| <i>Partial blood examination³</i> | | X | X | | |
| <i>Dipstick proteinuria</i> | X | X | X | | |
| <i>Collection of a paraffin-embedded tissue sample</i> | X | | | | |
| <i>Collection of blood samples</i> | | X | | X ⁴ | |
| <i>Adverse events and toxicity</i> | | | X ⁵ | | X ⁶ |
| <i>Survival follow up</i> | | | | | X |

1. Until the 2nd evidence of disease progression

2. Blood count and differential, bilirubin (total and direct), AST, ALT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium), International normalized ratio (INR)/Activated partial Thromboplastin Time (APTT), CEA, CA19.9; pregnancy test (if clinically indicate);

3. Blood count and differential, bilirubin (total and direct), serum creatinine, INR/APTT (only for patients on anticoagulation therapy);

4. Only a the first and second evidence of PD

5. AE assessment to be started after signing of IC until 30 days after last study treatment

6. Follow up on adverse events still ongoing at the time of 2nd PD

Dose reductions and delays for chemotherapeutic agents

| TOXICITY AT THE START OF SUBSEQUENT CYCLES OF THERAPY | GRADE/ Values | Irinotecan | Oxaliplatin | 5FU |
|--|---------------------------|------------------------------|--------------------|-------------|
| WBC | < 3.000/mm ³ | Hold until resolution | | |
| Neutrophils | < 1.000/mm ³ | | | |
| Platelets | < 100.000/mm ³ | | | |
| Diarrhea | ≥ 1 | | | |
| Mucositis | ≥ 1 | | | |
| Any other non-hematological toxicity | ≥ 2 | | | |
| Hand/foot syndrome | 3-4 | 100% | 100% | STOP |
| Neurotoxicity | ≥ 3 | 100% | STOP | 100% |
| PREVIOUS TOXICITY | | | | |
| | GRADE | Irinotecan | Oxaliplatin | 5FU |
| Neutropenia >5 days | 4 | 75% | 75% | 100% |
| Febrile Neutropenia | 4 | | | |
| Thrombocytopenia | 3-4 | | | |
| Diarrhea | 3 | 75% | 100% | 75% |
| Diarrhea | 4 | 50% | 100% | 50% |
| Stomatitis | 3 | 100% | 100% | 75% |
| Stomatitis | 4 | 100% | 100% | 50% |
| Myocardial Ischemia | NA | 100% | 100% | STOP |

Dose reductions and delays for bevacizumab

| Event | Grade | Adjustment to bev |
|--|--|---|
| Hypertension | 3 | If not controlled by 3-drug medication, permanently discontinue |
| | 4 (Hypertensive crisis and encephalopathy) | Permanently discontinue |
| Hemorrhage | Any grade CNS | Permanently discontinue |
| | ≥2 (pulmonary) | Permanently discontinue |
| | ≥3 (non-pulmonary/non-CNS) | Permanently discontinue |
| Venous thrombosis | 3 | Hold temporarily |
| | 4 | Permanently discontinue |
| Arterial thrombosis | Any Grade | Permanently discontinue |
| Congestive Heart Failure | ≥ 3 | Permanently discontinue |
| Proteinuria | 2-3 | - For 2+ dipstick: may administer bev, obtain 24-hour urine sample prior to next bev dose Suspend bev for ≥2 g /24 hours and resume when proteinuria is <2 g /24 hours and protein creatinine ratio <2.0 - For 3+ dipstick: obtain 24 hour urine sample prior to bev administration Suspend bev for ≥2 g /24 hours and resume when proteinuria is <2 g /24 hours and protein creatinine ratio <2.0 |
| | 4 | Permanently discontinue |
| GI perforation | Any grade | Permanently discontinue |
| PRES/RPLS | Any grade | Permanently discontinue |
| Fistula | Any grade TE fistula | Permanently discontinue |
| | ≥3 (other than TE) | Permanently discontinue |
| Febrile neutropenia/ thrombocytopenia | 4 | Hold temporarily |
| Other unspecified bev-related AE | 3 | Hold until recovery to ≤ Grade 1 |
| | 4 | Permanently discontinue |

Total number of centers

About 60 Italian Oncology Units

Study length

Study length is planned to be about 4.5 years since the enrollment is expected to be about 3 years, with a minimum period of follow-up of 18 months

Enrollment and data management

Registration, randomization and data collection are centralized at Ufficio Sperimentazioni Cliniche - Unit of Oncology, Azienda Ospedaliero-Universitaria Pisana and Clinical Trials Coordinating Center Istituto Toscano Tumori

14.2. RECIST 1.1

Response and progression will be evaluated in this study using the RECIST criteria version 1.1. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used.

Measurable Disease

Tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest x-ray
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability. All tumor measurements must be recorded in millimetres (or decimal fractions of centimetres). Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions

(longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are >5 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present”, “absent” or in rare cases “unequivocal progression”.

Best Response: All subjects will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to < 10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target

lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute progressive disease.

Table 1: Response for patients with Target and Non-Target Lesions

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|----------------|-----------------------------|-------------|------------------|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| PD | Any | Yes or No | PD |
| Any | Any | Yes | PD |
| Any | PD | Yes or No | PD |

Table 2: Response for patients with Non-Target Lesions only

| Non-Target Lesions | New Lesions | Overall Response |
|---------------------------|--------------------|-------------------------|
| CR | No | CR |
| Non-CR/Non-PD | No | Non-CR/non- PD* |
| Not evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* Non-CR/non-PD is preferred over “stable disease” for non-target disease.

Methods of Measurement - The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions - Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray - Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, chest CT is preferable.

CT / MRI - CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

14.3. NCI Common Terminology Criteria for Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 4.0 for toxicity and serious adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP home page:

http://ctep.cancer.gov:protocolDevelopment:electronic_applications:ctc.htm - ctc 40)

All appropriate treatment areas should have access to a copy of the CTC Version 4.0.

14.4 SAE report form

Please send completed form to tribe2study@gmail.com

Serious Adverse Event Report Form

TRIBE2 study

EUDRACT 2014-004436-19

SPONSOR USE ONLY

Receipt date of this report
(stamp or date)

TYPE OF REPORT

Initial Follow-up

A. REPORTER INFORMATION

| | | | |
|--|--|---|------|
| Reporter's First Name | | Reporter's Last Name | |
| Investigator's First Name (if different from Reporter) | | Investigator's Last Name (if different from Reporter) | |
| Address | | | City |
| Country | | Phone Number | |
| E-Mail: | | Fax Number | |

B. SUBJECT INFORMATION

| | | | |
|---|--|--------------|--------------|
| Subject ID | | | |
| _____ / _____ / _____ Study name Center name. Patient code | | | |
| Subject Initials | Sex <input type="checkbox"/> Female <input type="checkbox"/> Male | Height cm | Weight kg |
| Date of Birth (dd/mmm/yyyy) OR Age at Time of Adverse Event (Specify unit, e.g. years months, etc.) / / | | | |
| Ethnicity/Race <input type="checkbox"/> American Indian/Alaska native <input type="checkbox"/> Asian <input type="checkbox"/> Black or African American <input type="checkbox"/> Caucasian/White <input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Native Hawaiian or other Pacific islander <input type="checkbox"/> other _____ | | | |

C. RELEVANT MEDICAL HISTORY

| Condition/Disorder | Start Date (dd/mmm/yyyy) | End Date (dd/mmm/yyyy) | Ongoing |
|--------------------|-----------------------------|---------------------------|--------------------------|
| | / / | / / | <input type="checkbox"/> |
| | / / | / / | <input type="checkbox"/> |
| | / / | / / | <input type="checkbox"/> |
| | / / | / / | <input type="checkbox"/> |
| | / / | / / | <input type="checkbox"/> |

D. CONCOMITANT MEDICATIONS

| Drug Trade Name | Single Dose | Frequency of Administration | Route | Start Date (dd/mmm/yyyy) | Stop Date (dd/mmm/yyyy) | Indication |
|-----------------|-------------|-----------------------------|-------|-----------------------------|----------------------------|------------|
| | | | | / / | / / | |
| | | | | / / | / / | |
| | | | | / / | / / | |
| | | | | / / | / / | |
| | | | | / / | / / | |

E. INVESTIGATIONAL MEDICINAL PRODUCT(S)

Indication of Investigational Medicinal Product(s)

1

Investigational Medicinal Product Name / Route of Administration:

Not yet administered:

Date of first administration:

(dd/mmm/yyyy) / /

Dose/Unit:

Date of most recent administration prior to SAE:

(dd/mmm/yyyy) / /

Dose/Unit:

Number of cycles prior to SAE:

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

Temporary discontinued on: ____ / ____ / ____ Event subsided? Yes No Unknown

..... If "yes", how long after cessation of treatment? _____

If temporary discontinued, restarted on: ____ / ____ / ____ . At previous dose? Yes No Unknown

..... Event subsequently reappeared? Yes No Unknown

Permanently discontinued on: ____ / ____ / ____

Dose Reduced on: ____ / ____ / ____ Event subsided? Yes No Unknown

Treatment Continued without Change

Not Applicable

Unknown

2

Investigational Medicinal Product Name / Route of Administration

Not yet administered:

Date of first administration:

(dd/mmm/yyyy) / /

(hh:mm) /

Dose/Unit:

Date of most recent administration prior to SAE:

(dd/mmm/yyyy) / /

(hh:mm) /

Dose/Unit:

Number of cycles prior to SAE:

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT
 Temporary discontinued on: ____ / ____ / ____ Event subsided? Yes No Unknown

..... If "yes", how long after cessation of treatment? _____

 If temporary discontinued, restarted on: ____ / ____ / ____ At previous dose? Yes No Unknown

 Event subsequently reappeared? Yes No Unknown

 Permanently discontinued on: ____ / ____ / ____

 Dose Reduced on: ____ / ____ / ____ Event subsided? Yes No Unknown

 Treatment Continued without Change

 Not Applicable

 Unknown

F. ADVERSE EVENT(S) (If there are more than three adverse events, reprint this page as many times as is necessary.)

| | | | |
|---|---|---|---|
| Report adverse event diagnosis (ses) , if not available provide sign(s) and symptom(s) | AE _____: | AE _____: | AE _____: |
| Onset Date and Time (dd/mm/yyyy hh:mm) | ____ / ____ / ____ : ____ | ____ / ____ / ____ : ____ | ____ / ____ / ____ : ____ |
| Resolution Date (dd/mm/yyyy) | ____ / ____ / ____ | ____ / ____ / ____ | ____ / ____ / ____ |
| Duration, if less than 24h | ____ <input type="checkbox"/> hr <input type="checkbox"/> min | ____ <input type="checkbox"/> hr <input type="checkbox"/> min | ____ <input type="checkbox"/> hr <input type="checkbox"/> min |

SEVERITY

| | | | | | | |
|---|----------------------------|---|----------------------------|---|----------------------------|---|
| Severity Grade Use either NCI-CTC grading OR Qualitative Scale | <input type="checkbox"/> 1 | <input type="checkbox"/> Mild | <input type="checkbox"/> 1 | <input type="checkbox"/> Mild | <input type="checkbox"/> 1 | <input type="checkbox"/> Mild |
| | <input type="checkbox"/> 2 | <input type="checkbox"/> Moderate | <input type="checkbox"/> 2 | <input type="checkbox"/> Moderate | <input type="checkbox"/> 2 | <input type="checkbox"/> Moderate |
| | <input type="checkbox"/> 3 | <input type="checkbox"/> Severe | <input type="checkbox"/> 3 | <input type="checkbox"/> Severe | <input type="checkbox"/> 3 | <input type="checkbox"/> Severe |
| | <input type="checkbox"/> 4 | <input type="checkbox"/> Life-threatening | <input type="checkbox"/> 4 | <input type="checkbox"/> Life-threatening | <input type="checkbox"/> 4 | <input type="checkbox"/> Life-threatening |
| | <input type="checkbox"/> 5 | <input type="checkbox"/> Death | <input type="checkbox"/> 5 | <input type="checkbox"/> Death | <input type="checkbox"/> 5 | <input type="checkbox"/> Death |

SERIOUSNESS

| | | | |
|--|---|---|---|
| Resulted in Death | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Is Life-Threatening | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Requires/Prolongs Hospitalization | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Persistent/Significant Disability/Incapacity | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medically Significant | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Is Congenital Anomaly/Birth Defect | Parent-Child/Foetus Report Form must be completed | Parent-Child/Foetus Report Form must be completed | Parent-Child/Foetus Report Form must be completed |

OUTCOME

| | | | |
|---|--------------------------------------|--------------------------------------|--------------------------------------|
| Unknown (only applicable if subject is lost to follow-up) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Fatal (AE resulted in death) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Ongoing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Resolved without Sequelae | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Resolved with Sequelae | <input type="checkbox"/> Specify: | <input type="checkbox"/> Specify: | <input type="checkbox"/> Specify: |

RELATION TO THE INVESTIGATIONAL MEDICINAL PRODUCT(S) / STUDY TREATMENT If an event is unrelated, please indicate any other causality factors in the appropriate section and/or provide further details in the narrative (Description of Adverse Event(s)).

| | | | | | | |
|-------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | Related | Unrelated | Related | Unrelated | Related | Unrelated |
| Investigational Medicinal Product 1 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Investigational Medicinal Product 2 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

G. DESCRIPTION OF ADVERSE EVENT(S)

Provide a detailed description of AE, i.e. clinical course of event(s), signs, symptoms, laboratory results, treatment of AE, etc.

1) In Case of Death

Cause of Death: AE Other If "other", specify:

Date of Death: ____ / ____ / ____ Autopsy performed? Yes No If "yes", please attach autopsy report if available.

2) In Case of Hospitalization or Prolonged Hospitalization

Admission Date: ____ / ____ / ____ Discharge Date: ____ / ____ / ____ Not Discharged

H. RELEVANT TESTS/PROCEDURES/LABORATORY TESTS TO CONFIRM ADVERSE EVENT

I. OTHER RELEVANT RISK FACTORS

- Alcohol Use
- Pace Maker
- Metabolic Disorders
- Implants
- Physical Therapy
- Drug Dependence
- Drug Abuse
- Other, specify: _____
- Contraceptive
- Radiation Therapy
- Obesity
- Smoking
- Diet
- Allergy

J. CAUSALITY FACTORS OTHER THAN TRIAL TREATMENT

- Concomitant Medication, please specify suspected drug: _____ (record details in section D)
- Medical History, please specify disease: _____ (record details in section C)
- Disease Under Study Disease Progression; specify: _____
- Trial Procedure Other; specify: _____

K. INVESTIGATOR SIGNATURE

Investigator's
Signature

Date of Report: