The AtezoTRIBE Study

RANDOMIZED PHASE II STUDY OF FOLFOXIRI PLUS BEVACIZUMAB PLUS ATEZOLIZUMAB VERSUS FOLFOXIRI PLUS BEVACIZUMAB AS FIRST-LINE TREATMENT OF UNRESECTABLE METASTATIC COLORECTAL CANCER PATIENTS

EUDRACT 2017-000977-35

PROTOCOL

TITLE:	Randomized phase II study of FOLFOXIRI plus BEVACIZUMAB plus ATEZOLIZUMAB versus FOLFOXIRI plus BEVACIZUMAB as first-line treatment of unresectable metastatic colorectal cancer patients.
PROTOCOL NUMBER:	AtezoTRIBE
VERSION NUMBER:	2.1
DATE FINAL:	19 Feb 2019
EUDRACT NUMBER:	2017- 000977-35
IND NUMBER:	NA
TEST PRODUCTS:	5 Fluorouracil, Oxaliplatin, Irinotecan, Bevacizumab, Atezolizumab,
MEDICAL MONITOR:	Prof. Alfredo Falcone
SPONSOR:	Fondazione GONO Via Goffredo Mameli 3/1 16122 - Genoa
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PROTOCOL SIGNATURE PAGE (SPONSOR)

I have read and understood the contents of the clinical protocol for Clinical Study AtezoTRIBE dated February 19th 2019 and agree to meet all obligations of GONO as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Investigators are informed of all relevant information becoming available during the conduction of this study.

Coordinator's signature

Prof. Alfredo Falcone

20/FEB/2019

Date

PROF. ALFREDO FALCONE
Presidente e Legale Rappr.te
G.O.N.O.
Gruppo Oncologico del Nord Ovest

PROTOCOL ACCEPTANCE FORM

TITLE:	Randomized phase II study of FOLFOXIRI plus BEVACIZUMAB plus ATEZOLIZUMAB versus FOLFOXIRI plus BEVACIZUMAB as first-line treatment of unresectable metastatic colorectal cancer patients.
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MEDICAL MONITOR:	Prof. Alfredo Falcone
SPONSOR:	Fondazione GONO
DATE FINAL:	February 19th , 2019

I confirm that I have read and understood the clinical trial protocol and will undertake my work according to the provisions stipulated in the protocol and in ethical principles found in the latest version of the Declaration of Helsinki, International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines and applicable legal requirements.

I agree to conduct the study in accordance with the current protocol

CHIARA CRENNONI

Principal Investigator's name (print)

20/Feb/2019

Principal Investigator's signature

Date

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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
ALT (SGPT): Alanine-Aminotransferase (Sèrum Glutamic Pyruvic Transaminase)
APTT: Activated Partial Thromboplastin Time
AST (SGOT): Aspartate-Aminotransferase (Sèrum Glutamic Oxaloacetic Transaminase)
Bas: at baseline
BBP: bevacizumab beyond progression
Bev: bevacizumab
CA19.9: Carbohydrate Antigen 19.9
CAPOX: Capecitabine, Oxaliplatin
CEA: CarcinoEmbryonic Antigen
CFI: chemotherapy-free interval
CHF: Congestive Heart Failure
CI: confidence interval
CNS: Central Nervous System
CR: Complete Response
CT: Computed Tomography
CTCAE: Common Terminology Criteria for Adverse Events
CVAD: Central Venous Access Device
DoR: Deepness of Response
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: Epidermial 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
fT3: free Triiodothyronine
fT4: free Thyroxin
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
irORR: immune-related Objective Response Rate
irPFS: immune-related Progression Free Survival
IRR: infusion-related reaction
irRC: immune-related Response Criteria
ISBN: International Standard Book Number
ITT: Intension To Threat
LDH: Lactate Dehydrogenase
LFT: liver function test
LOHP: oxaliplatin
LV: leucovorin
mAb: monoclonal anti-body
mCRC: metastatic colorectal cancer
MDSC: myeloid-derived suppressor cell
MRI: Magnetic Resonance Imaging
MSI: microsatellite instability
NA: Not Available
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
NCIC-CTG: National Cancer Institute of Canada – Clinical Trials Group
NSCLC: non-small cell lung cancer
NYHA: New York Heart Association
OFI: oxaliplatin-free interval
ORR: Objective Response Rate
OS: overall survival
pCR:pathologic Complete Response
PD: Progression Disease
PD-1: Programmed Death-1
PD-L1: Programmed Death Ligand-1
PDGF: Platelet-derived Growth Factor
PFS: Progression Free Survival
PlGF: Placental Growth Factor
PR: Partial Response
PRES/RPLS: Posterior Reversible Encephalopaty 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
SIRS: systemic inflammatory response syndrome
SIA: systemic inflammatory activation
SMC: Safety Monitoring Committee
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
TSH: Thyroid-Stimulating Hormone
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

SYNOPSIS

Title

Randomized phase II study of FOLFOXIRI plus BEVACIZUMAB plus ATEZOLIZUMAB versus FOLFOXIRI plus BEVACIZUMAB as first-line treatment of unresectable metastatic colorectal cancer patients**.**

Version

2.1 dated February 19th, 2019

Sponsor

Fondazione GONO

Coordinating Investigator

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Phase

Phase II randomized

Indication

Metastatic colorectal cancer (mCRC)

Primary objective

Primary objective of this study is to evaluate the efficacy of the addition of atezolizumab to FOLFOXIRI plus bev as first line treatment of patients with metastatic colorectal cancer in terms of Progression Free Survival (PFS).

Secondary objectives

Secondary objectives of this study are to assess the safety, activity and efficacy of the addition of atezolizumab to FOLFOXIRI plus bev in terms of:

- Overal toxicity rate
- Toxicity rate
- Objective response rate according to RECIST version 1.1 criteria (ORR)
- Immuno-related objective response rate according to modified RECIST criteria (irORR)
- Early Objective Response Rate (EOR)
- Deepness of response (DoR)
- R0 Resection Rate
- Progression Free Survival 2 (PFS2)
- 2nd-PFS
- Time to failure of strategy (TFS)
- Overall Survival (OS)
- Translational analyses including the evaluation of immunity-related parameters on samples collected both before and after the treatment.

Definition of the primary endpoint

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.

Definition of secondary endpoints

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 5.0), 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 5.0), during the induction and the maintenance phases of treatment.

Objective Response Rate (ORR) 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.

Immuno-related Objective Response Rate (irORR) is defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to immune-modified RECIST 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 (EOR) is defined as the percentage of patients, relative to the total of the enrolled subjects, achieving a ≥ 20% decrease in the sum of diameters of RECIST target lesions at week 8 compared to baseline.

Deepness of Response (DoR) is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, when compared with 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.

Progression Free Survival 2 (PFS2) is defined as beginning with randomization and ending with the first of the following events: a) death; b) disease progression according to RECIST 1.1 criteria 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 metastasis will not result in censoring for PFS2.
PFS2 will be analyzed both in the intention-to-treat population (whichever 2nd-line treatment will be adopted) and in the per-protocol population.

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 according to RECIST 1.1 criteria 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.

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.

Study design

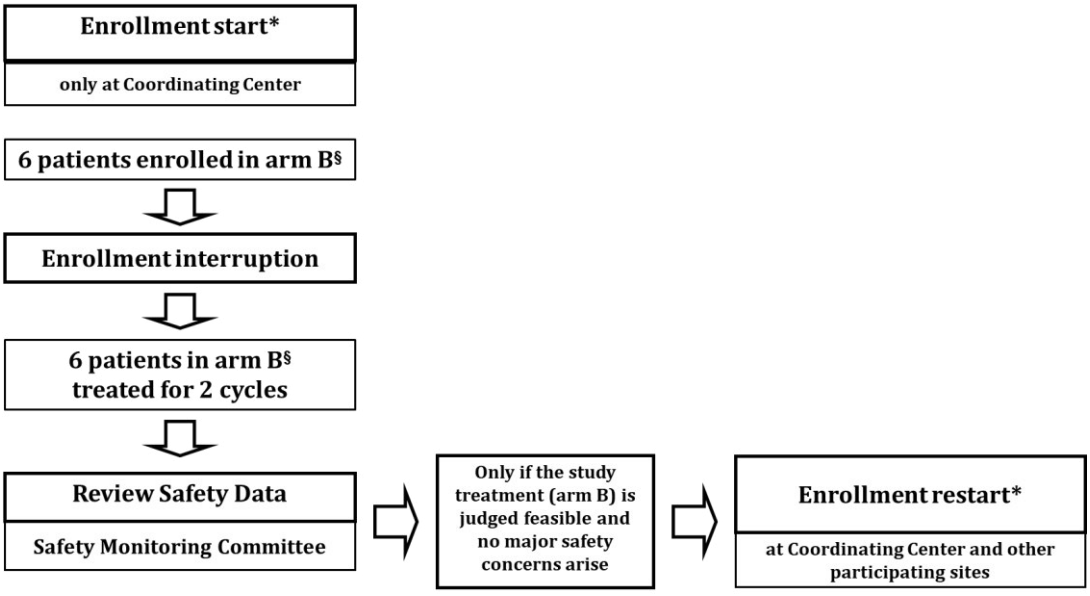
This is a prospective, open-label, multicentric phase II randomized in a 1:2 ratio trial in which patients initially unresectable and previously untreated mCRC will receive induction treatment with FOLFOXIRI plus bev up to 8 cycles followed by maintenance with 5-FU/LV plus bev until disease progression, unacceptable toxicity or patient's refusal (arm A) versus FOLFOXIRI plus bev plus atezolizumab up to 8 cycles followed by maintenance with 5-FU/LV plus bev plus atezolizumab until disease progression, unacceptable toxicity or patient's refusal (arm B). If disease progression does not occur during induction, at the treating physician's discretion, the reintroduction after progression of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.

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

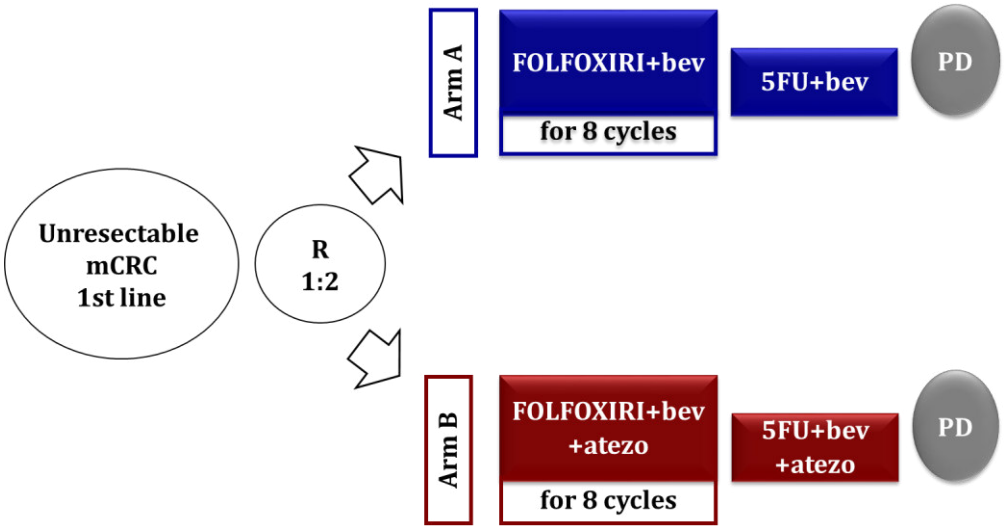
Safety run-in phase

The study will be initially conducted at the Coordinating Center (Department of Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa) until 6 patients will randomly assigned to arm B. At that time, the enrollment of new patients will be temporary interrupted. When 6 patients enrolled in arm B will receive 2 cycles of study treatment, a Safety Monitoring Committee (SMC) will review unblinded safety data (including demographics, adverse events, serious adverse events, adverse events of special interest and relevant laboratory data).

The SMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor. The enrolment will then resume and involve approximately 28 additional centers, only if the study treatment combination will be judged feasible and no major safety concerns will arise.



***for patients' allocation and study schema, see below. §: experimental arm, see below.**



mCRC: metastatic colorectal cancer; bev: bevacizumab; 5FU: 5-fluorouracil; atezo: azetolizumab; PD: progressive disease.
Stratification factors: Center; ECOG Performance status: 0 *versus* 1-2; primary tumor location: right *versus* left or rectum; previous adjuvant chemotherapy: yes *versus* not.

Number of patients

Approximately 201 patients with initially unresectable and previously untreated metastatic CRC will be enrolled in this study.

Inclusion criteria

- Written informed consent to study procedures
- 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 < or = 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 x 109/L, Platelets >100 x 109/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 x UNL (or <5 x UNL in case of liver metastases) alkaline phosphatase <2.5 x UNL (or <5 x UNL in case of liver metastases)
- Creatinine clearance ≥50 mL/min or serum creatinine 1.25 x UNL
- INR or aPTT ≤1.5 × ULN. Patients who are on therapeutic doses of anti-coagulants are eligible if they are on a stable dose of anti-coagulant for 28 days with stable INR and PTT values
- 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
- Male subjects with female partners of childbearing potential must be willing to use adequate contraception as outlined in Section 5.5 – Contraception, starting with the first dose of study therapy through 6 months after the last dose of bevacizumab and within 5 months after the last dose of atezolizumab.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

- 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 continuous months, are surgically sterile, or are sexually inactive.
- Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.5 – Contraception, for the course of the study starting with the first dose of study therapy through 6 months after the last dose of bevacizumab and within 5 months after the last dose of atezolizumab.
- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject
- Will and ability to comply with the protocol

Exclusion criteria

- Radiotherapy to any site within 4 weeks before the study
- Previous adjuvant oxaliplatin-containing chemotherapy
- Previous treatment with bevacizumab
- Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
- Untreated brain metastases or spinal cord compression or primary brain tumours
- History or evidence upon physical examination of CNS disease unless adequately treated
- Hystory of haemoptysis ≥2 grade NCIC-CTG criteria within one month prior screening
- Active or untreated CNS metastases. Patients with a history of treated asymptomatic CNS metastases are eligible provided they meet all the following criteria:
    - ✓ Measurable disease outside the CNS
    - ✓ Only supratentorial or cerebellar metastases allowed (i.e. no metastases to midbrain, pons, medulla or spinal cord)
    - ✓ No ongoing requirement for corticosteroid therapy for CNS disease
- 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 histor 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.

- Active infection requiring antibiotics at the time of initiation of study treatment.
- Any previous venous thromboembolism ≥ NCI CTCAE Grade 4.
- 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
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to initiation of study treatment
- 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 dose of bevacizumab and within 5 months after the last dose of atezolizumab.
- History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis,

Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

- ✓ Note: History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
- ✓ Note: Controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

• History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

- ✓ Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted

• Positive test for human immunodeficiency virus (HIV)

• Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C

- ✓ Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
- ✓ Note: Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

• Active tuberculosis

• Prior allogenic bone marrow transplantation or solid organ transplant

• Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to start of study treatment, or requirement for systemic immunosuppressive medications during the trial. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

- ✓ Note: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study.

- Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the atezolizumab formulation
- Administration of a live, attenuated vaccine within 4 weeks prior to start of study treatment or anticipation that such a live attenuated vaccine will be required during the study
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study treatment
- If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

Study treatment

Arm A – 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, followed by
- Irinotecan 165 mg/sqm iv over 60 minutes day 1, followed by
- Oxaliplatin 85 mg/sqm iv over 2 hours day 1, in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours day 1, followed by
- 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-FU is interrupted because of adverse events, patient's refusal or investigator's choice.

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

- Atezolizumab 840 mg iv over 30 minutes(60 minutes at the first infusion) day 1, followed by
- Bevacizumab 5 mg/kg iv over 30 minutes day 1, followed by
- Irinotecan 165 mg/sqm iv over 60 minutes day 1, followed by
- Oxaliplatin 85 mg/sqm iv over 2 hours day 1, in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours day 1, followed by
- 5-fluorouracil 3200 mg/sqm 48 h-continuous infusion, starting on day 1

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

In both arms, if disease progression does not occur during induction with FOLFOXIRI plus bev +/- atezolizumab, at the treating physician's discretion, the reintroduction after progression of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.
In the case of persistent neurotoxicity ≥ G2, FOLFIRI plus bev +/- atezolizumab will be administered for a maximum of 8 cycles.

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

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

Statistical considerations

The primary analysis of PFS will be performed in the ITT population. The Kaplan-Meier approach will be used to estimate PFS and the 1-sided log-rank test will be adopted to compare study arms. A log-rank test stratified by the same factors as used for randomization will also be performed, as well as a multivariable model including all the significant baseline variables.

Based on the assumption that PFS of each arm follows an exponential distribution and considering an expected median PFS of 12 months for standard arm, 129 events are required to detect a hazard ratio (HR) for PFS of 0.66 in favour of the experimental group (arm B), with a one-sided unstratified log-rank test, with α and β errors of 0.10 and 0.15, respectively. Assuming an accrual rate of 210 subjects/year, a 1:2 randomization and a minimum follow up period equal to 1.5 years, a total of 201 patients should be randomized (arm A/B: 67/134).

Procedure	Screening (within 28 days before random)	Baseline	Before every cycle[1]	Every 8 wks [1]	After the 2nd evidence of PD
Informed Consent	X				
Complete medical history	X				
Inclusion/Exclusion Criteria Checked	X				
Tumor assessment (total-body CT or abdomen MRI + chest CT)	X			X	
Collection of a CD-ROM copy of CT scan	X			X	
12-lead ECG	X				
ECOG PS	X	X	X	X	
Physical examination	X		X	X	
Complete blood examination[2]	X			X	
Partial blood examination[3]		X	X		
Sierology[4]	X				
Dipstick proteinuria	X	X	X		
Blood pregnancy test	X[5]				
Collection of paraffin-embedded tissue samples (central tumor and invasive margin)	X[6]				
Collection of blood samples		X	X[7]	X[8]	
Collection of feces samples		X		X[9]	
Adverse events and toxicity	X[10]	X	X	X	X[11]
Survival follow up					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), TSH, fT3, fT4, amylase, lipase, 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), AST/ALT, serum creatinine. INR/APTT only for patients on anticoagulation therapy;
4. HIV, HBV, HCV;
5. Only for women of childbearing potential;
6. Paraffin-embedded samples will be collected also for tissues resected after the treatment, when available;

7. Only at the second cycle;
8. Only at the end of first induction treatment, and at the first and second evidence of PD;
9. Only at the end of first induction treatment, and at the first evidence of PD
10. AE assessment to be started after signing of IC until 90 days after last study treatment;
11. Follow up on adverse events still ongoing at the time of 2nd PD

Total number of centers

About 30 Italian Oncology Units.

Study length

Study length is planned to be about 30 months since the enrollment is expected to be about 12 months, with a minimum period of follow-up of 18 months.

Enrollment and data management

Registration, randomization and data collection are centralized at the coordinating center of Fondazione GONO.

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 a 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).

Based on efficacy results of TRIBE trial [15], FOLFOXIRI plus bev is now recommended by all major guidelines as safe and efficacious first-line therapeutic option in selected mCRC patients [17, 18].

1.2. 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 [19], 2 [20], COIN [21] and GISCAD [22] 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) [23].

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) [24].

In the AIO0207 trial is a non-inferiority study where patients without progression after 6 months of treatment with fluoropyrimidine, oxaliplatin and bev were randomized among one of following arms: fluoropyrimidine plus bev, bev alone or observation. Upon the first disease progression, the same induction treatment had to be reintroduced and continued until the second evidence of disease progression. The primary endpoint was the TFS, defined as the time from randomization to progression upon re-introduction of the same induction treatment; standard treatment was fluoropyrimidine plus bev. The boundary for assessment of non-inferiority was upper limit of the one-sided 98.8% CI 1.43. The non-inferiority of the observation strategy was not demonstrated (HR 1.26 [0.99–1.60]; p=0·056; upper limit of the one-sided 98·8% CI 1.65), whereas the non-inferiority of bev strategy was demonstrated (HR 1.08 [95% CI 0·85–1·37]; p=0·53; upper limit of the one-sided 98·8% CI 1.42) [25].

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.

1.3. Re-introduction of first-line induction regimen after disease progression

The opportunity to alternate induction and phases of de-intensified therapy makes more clinically and biologically sound the re-introduction of agents used during the induction phase after the occurrence of disease progression [17].

A pooled analysis of OPTIMOX1 and 2 studies identified a sensitive population of patients more likely to benefit from the re-introduction of an oxaliplatin-based therapy by considering the efficacy of the induction therapy followed by an oxaliplatin-free interval (OFI) of at least 6 months between two periods of oxaliplatin-based therapy [26].

A recent pooled analysis has been focused on treatments received after disease progression to upfront therapy with FOLFOXIRI plus bev in a cohort of 482 patients enrolled in TRIBE and MOMA trials [27]. The main aim was to evaluate the outcome of treatments administered after first-line progression, in terms of 2ndPFS (time from 2nd line therapy start to disease progression or death) and OS II (time from 2nd line therapy start to death). For patients in which the same drugs used in first-line were totally or partially reintroduced, the chemotherapy-free interval (CFI, time from the last administration of irinotecan or oxaliplatin during first-line to disease progression) was calculated.

Out of 429 patients experienced disease progression, 303 (70.6%) received a 2nd line treatment: 93 FOLFOXIRI +/- bev (Group A), 119 FOLFOX/XELOX or FOLFIRI +/- bev (Group B) and 91 other therapy (Group C), including an anti-EGFR moAb in 60 cases. No difference was observed among the three groups in terms of 2ndPFS (median 2nd PFS Group A: 5.6 vs Group B: 4.4 vs Group C: 3.9 mos; p= 0.60) or OS II (median OS II Group A: 14.9 vs Group B: 13.8 vs Group C: 11.7 mos; p=0.49). In the subgroup of patients with a CFI < 6 mos, Group A (n = 52) reported longer 2ndPFS compared to both Group B (n = 58) (median 2ndPFS 5.3 vs 3.0 mos; HR: 0.61, 95%CI 0.41-0.89; p=0.009) and Group C (n = 58) (5.3 vs 3.2 mos; HR: 0.71, 95%CI 0.48-1.05; p=0.07). Consistent results were achieved in OS II (Group A vs Group B; median OS 13.6 vs 10.8 mos; HR: 0.65, 95%CI 0.42-1.00; p=0.053; Group A vs Group C 13.6 vs 8.9 mos;

HR: 0.60, 95%CI 0.39-0.93; p=0.002). In the subgroup of pts with a CFI ≥ 6 mos, no significant difference was shown between Group A (n = 41) and Group B (n = 61) or C (n = 33). Taken together, these results demonstrated that treatments after progression to first-line FOLFOXIRI plus bev are feasible and show expected efficacy results. In particular, the re-introduction of the triplet plus bev seems more effective than doublets plus bev or other treatment when a more aggressive disease biology is suggested (CFI < 6 mos).

Based on these data, the re-introduction of an initially successful induction regimen after the occurrence of progression is regarded as a treatment option following a maintenance strategy, as long as no relevant residual toxicity is present.

1.4. Continuation of bevacizumab beyond progression in mCRC

Preclinical studies 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) [28].

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 [29]. 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 [30].

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 [31].

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.

1.5. Atezolizumab

Atezolizumab (MPDL3280A) [32-34] is a humanized monoclonal immunoglobulin G1 targeting Programmed Death-Ligand 1 (PD-L1), and thus inhibiting its interaction with Programmed Death 1 (PD-1) and B7.1. PDL-1 is expressed on both tumour cells across a broad range of human tumours and in the tumour microenvironment. Since the binding of PD-L1 with PD-1 and B7.1 inhibits T-cells proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumour-specific T-cell immunity. Inhibition of PD-L1 signalling by atezolizumab demonstrated clinical activity in a wide range of solid tumours in early clinical trials [35-37]. Even if overexpression of PD-L1 on tumor cells has been

reported to impede anti-tumor immunity, conflicting data were reported regarding the correlation between expression of PD-L1 on both tumour cells and tumour microenvironment and efficacy of anti-PD1/PD-L1 agents [38-43].

In trials investigating atezolizumab both as a single agent [44] and when used in combination with cytotoxic agents [45-47], including 5-fluoruracil, oxaliplatinum, carboplatinum, paclitaxel, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. No maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of adverse events have been determined. As a single agent, grade 3 or 4 adverse events were reported in 12% of patients and deaths related to atezolizumab were observed in 4 patients. When atezolizumab was administered in combination to chemotherapy, the adverse events were consistent with the known safety profile of each agent (atezolizumab monotherapy and chemotherapy) and no additive effects were observed when atezolizumab was administered with chemotherapy. Fatigue, decreased appetite, nausea, diarrhea, pyrexia and cough were the most commonly reported adverse events in single and combination therapy. The overall immune-mediated adverse events reported for atezolizumab were considered moderate in severity and majority of patients were able to continue on atezolizumab therapy. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored, including potential dermatologic, hepatic, endocrine, gastrointestinal and respiratory events, with no major concerns.

In two phase II prospective trials atezolizumab in monotherapy showed durable activity in urothelial carcinoma progressed after a platinum-based chemotherapy [48] and improved survival compared with docetaxel in patients with previously treated NSCLC [49]. In both studies, atezolizumab was well tolerated with an expected safety profile. Many other trials of atezolizumab in association with chemotherapy in several tumours types are ongoing. The recommended dose of atezolizumab is 1200 mg administered intravenously every 3 weeks; nevertheless, for administration with agents on a 14– or 28-day cycle, a dose of 840 mg atezolizumab

administered every 2 weeks has the equivalent dose exposure as the 1200 mg every 3 weeks (21–day cycle) and is currently adopted in several trials [50-54].

1.6. Immunotherapy in metastatic colorectal cancer

While immunotherapy has already reported relevant achievements in other solid malignancies (i.e. metastatic melanoma, metastatic non-small cell lung cancer, metastatic renal cancer) [38-43], less evidence is currently available in mCRC. Promising results were reported with the anti-PD-1 pembrolizumab in chemorefractory microsatellite instability (MSI) high mCRC patients [55]. In particular immune-related objective response rate (irORR) and 20-week immune-related progression-free survival rate were 40% and 78% respectively for mismatch repair–deficient colorectal cancers and 0% and 11% for mismatch repair–proficient colorectal cancers, showing that mismatch-repair status predicted clinical benefit of immune checkpoint blockade. This preferential effect of checkpoint inhibitors on MSI-high CRCs has been postulated to be due to an increase in neo-antigens from a greater somatic mutation load. One potential mechanism to convert otherwise resistant cancers is to recruit immune cells to the tumor sites. In preclinical experiences, both chemotherapy and available targeted agents, in particular bevacizumab, demonstrated immunological effects. Indeed VEGF blockade raises lymphocyte adhesion to vessel walls, thus contributing to increased immune cell recruitment to the tumor site, reduces T-reg lymphocytes in the tumor, stimulates the maturation of dendritic cells and reduces the expansion of T-reg lymphocytes and myeloid-derived suppressor cells (MDSC) [56-59]. Also chemiotherapic agents active against colorectal cancer show immunogenic effects: 5-FU reduces tumor-associated MDSCs and increases CD8 tumor-infiltrating lymphocytes [60], while oxaliplatin induces immunogenic cell death (calreticulin exposure, release of ATP and HMGB1) [61, 62]. Therefore chemotherapy and bev could impact the tumor immune microenvironment leading to increase CD8 positive-T-cell infiltration and the anti-PD-L1 can be effective in activating the local immune system against the cancer cells. In addition, atezolizumab is an anti-PD-L1 mAb, which is capable of inhibiting the interaction of

PD-L1 with PD-1 and also PD-L1 with B7-1 with a possible wider immunomodulatory effect respect to anti-PD-1 agents [32-34].

Extremely encouraging efficacy and safety results were reported in a phase Ib study of FOLFOX plus bev plus atezolizumab as first-line treatment of mCRC patients [46]. More frequent grade ≥3 adverse events were neutropenia (32%), diarrhea (11%), abdominal pain (9%), increased AST/ALT (7%), hyperbilirubinemia (5%), pneumonia (5%) and pulmonary embolism (5%). No unexpected adverse events or exacerbation of chemotherapy- or bev-related toxicities were reported. In patients treated in first-line, objective response rate was 48% and for responding patients, progression-free survival ranged from 10 to 61 weeks. Significant immune activation was observed both at tissue and plasma level in treated patients: an increase in CD8+ cell infiltration, PD-L1 expression and T effector gene signature expression in tumour tissue and an increase in the frequency of activated CD8+ T cells in the periphery were observed after treatment.

1.7. Continuation of atezolizumab beyond progression

Although RECIST-defined disease progression is considered failure of treatment for non-immunotherapeutic agents, resulting in treatment discontinuation, in different trials investigating immune-based therapeutics, some patients whose disease met the criteria for disease progression based on RECIST v1.1 showed late but deep and durable responses [63].

The observation of delayed immune-related responses suggested that patients could benefit from continued treatment with immune checkpoint inhibitors beyond the evidence of RECIST-defined disease progression.

Retrospective analyses of the efficacy and safety of nivolumab administered beyond progression in patients with renal cell carcinoma [64, 65] and in patients with advanced melanoma [66] suggested that a proportion of patients derived apparent clinical benefit, without compromising safety.

With regard to atezolizumab, a post-hoc analysis of the phase III randomized OAK trial, evaluating the efficacy of docetaxel vs atezolizumab in pre-treated patients

affected by metastatic non-small cell lung cancer (NSCLC), reported promising data about the use of this anti-PD-L1 antibody beyond progression [67]. Out of 332 patients who experienced RECIST disease progression in the atezolizumab arm, 168 patients (51%) continued the immune modulator post-progression. According to RECIST, 12 (7%) and 83 (49%) patients achieved partial response and disease stabilization, respectively, thus achieving a disease control rate of 57%. The clinical benefit was confirmed by post-progression OS results, reaching a median OS post-PD of 12.7 mos (95% CI: 9.3-14.9). Furthermore, atezolizumab beyond progression showed a tolerable safety profile and was not associated with increased safety risk (6% of patients experienced grade ≥3 adverse events).

Efficacy and safety outcomes of the use of atezolizumab beyond progression have been recently described in a *post-hoc* analysis of the phase II single-arm IMvigor210 study [68], in which 310 patients previously platinum-treated with locally adavanced or metastatic urothelial carcinoma received the anti-PD-L1 monotherapy until loss of clinical benefit, with similar exposure–adjusted adverse event frequencies before and after progression.

Taken together, these data suggest that patients treated beyond their first disease progression can experience a prolonged clinical benefit with continued atezolizumab treatment, with no new or unexpected adverse events. The continuation of atezolizumab may also enhance the efficacy of the re-introduction of triplet plus bevacizumab.

2. STUDY RATIONALE

• The TRIBE study demonstrated a significant advantage in terms of PFS, RR and OS for the combination of FOLFOXIRI and bev when compared with the doublet FOLFIRI plus bev, as first-line treatment of unresectable mCRC patients.

• 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.

• Atezolizumab (MPDL3280A) is a humanized monoclonal immunoglobulin G1 targeting PD-L1. Inhibition of PD-L1 signalling by atezolizumab demonstrated clinical activity in a wide range of solid tumours in early clinical trials.

• In trials investigating atezolizumab both as a single agent and when used in combination with cytotoxic agents, including 5-fluoruracil, oxaliplatin, carboplatin, paclitaxel, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs.

• Extremely encouraging efficacy and safety results were reported in a phase Ib study of FOLFOX plus bev plus atezolizumab as first-line treatment of mCRC patients. In particular a manageable safety profile and no unexpected adverse events or exacerbation of chemotherapy- or bev-related toxicities were observed.

Based on these considerations we designed the present phase II randomized study of first-line FOLFOXIRI plus bev (arm A) versus FOLFOXIRI plus bev plus atezolizumab (arm B) as first-line treatment of mCRC, in order to assess the combination of immunoterapic agent with an intensified chemotherapy regimen (i.e. the triplet FOLFOXIRI) plus bevacizumab. This treatment may represent an innovative and efficacious approach to enhance the efficacy of atezolizumab by exploiting the immunogenic properties of both chemotherapy and bev. Patients will be randomized in a 1:2 ratio to enter the standard treatment (arm A) or the experimental treatment

(arm B). Stratification factors will be: center, ECOG PS (0 vs 1, 2), primary tumor location (right vs left or rectum) and previous adjuvant chemotherapy. Patients will receive up to 8 cycles of induction with FOLFOXIRI plus bev or FOLFOXIRI plus bev plus atezolizumab according to randomized arm, followed by maintenance with 5-fluorouracil/L-leucovorin (5-FU/LV) plus bev or 5-FU/LV plus bev plus atezolizumab until disease progression, unacceptable toxicity or patient's refusal.

If disease progression does not occur during induction, at the treating physician's discretion, the reintroduction after progression of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.

3. STUDY DESIGN

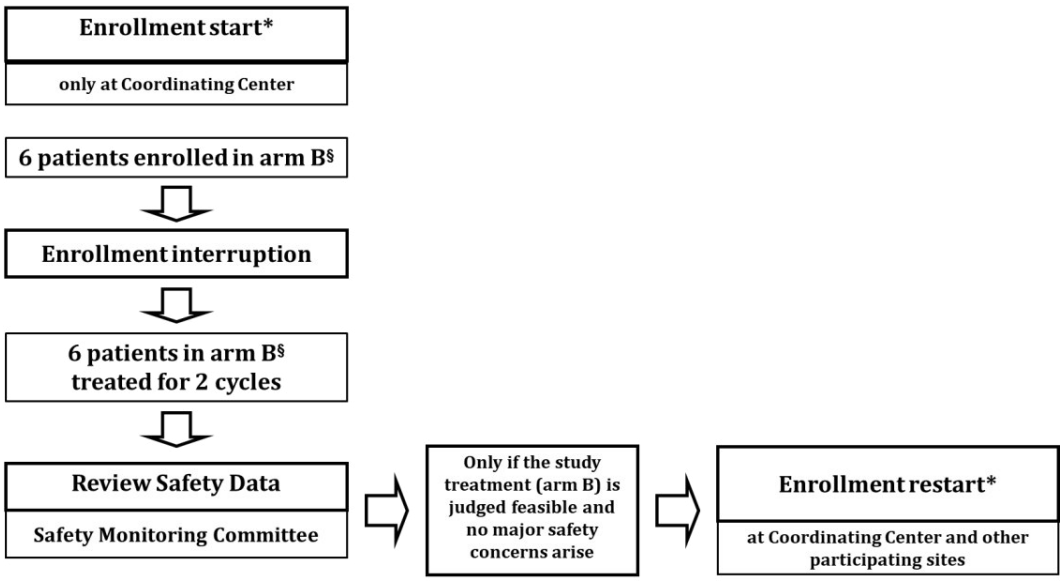
This is a prospective, open-label, multicentric phase II randomized in a 1:2 ratio trial in which patients initially unresectable and previously untreated mCRC will receive induction treatment with FOLFOXIRI plus bev up to 8 cycles followed by maintenance with 5-FU/LV plus bev until disease progression, unacceptable toxicity or patient's refusal (arm A) versus FOLFOXIRI plus bev plus atezolizumab up to 8 cycles followed by maintenance with 5-FU/LV plus bev plus atezolizumab until disease progression, unacceptable toxicity or patient's refusal (arm B). If disease progression does not occur during induction, at the treating physician's discretion, the reintroduction after progression of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.

3.1. Safety run-in phase

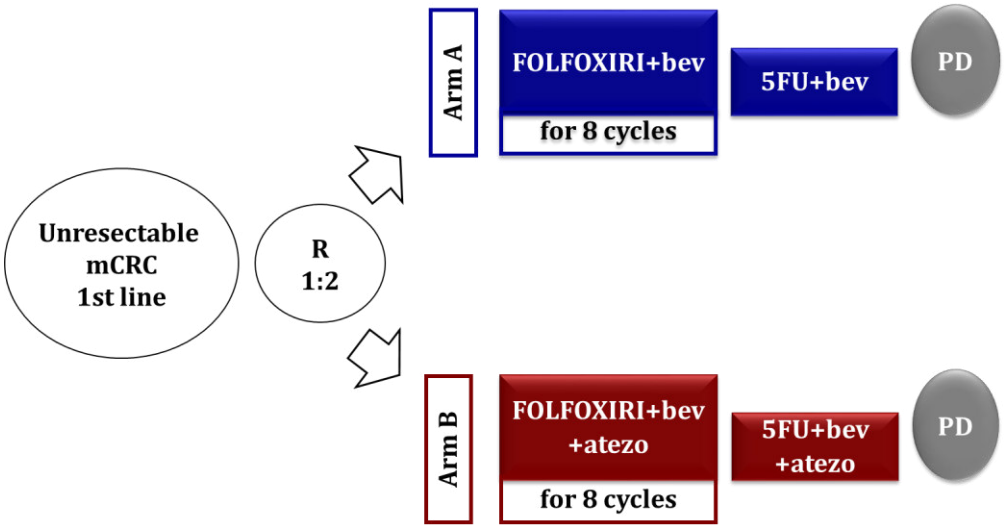
The study will be initially conducted at the Coordinating Center (Department of Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa) until 6 patients are randomly assigned to arm B. At that time, the enrollment of new patients will be temporary interrupted. When 6 patients enrolled in arm B receive 2 cycles of study treatment, a Safety Monitoring Committee (SMC) will complete a safety evaluation.

The enrollment will then resume and involve approximately 28 additional centers, only if the study treatment combination is judged feasible and no major safety concerns arise.

The study design is displayed below.



***for patients' allocation and study schema, see below. §: experimental arm, see below.**



mCRC: metastatic colorectal cancer; bev: bevacizumab; 5FU: 5-fluorouracil; atezo: azetolizumab; PD: progressive disease.
Stratification factors: Center; ECOG Performance status: 0 *versus* 1-2; primary tumor location: right *versus* left or rectum; previous adjuvant chemotherapy: yes *versus* not.

If disease progression does not occur during induction, at the treating physician's discretion, the reintroduction of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.

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

3.2. Safety Monitoring Committee

A Safety Monitoring Committee (SMC), including three academic experts not directly involved in the trial conduction, will early evaluate the safety of the experimental treatment (arm B).

Unblinded safety data will be firstly reviewed by the SMC when 6 patients in arm B receive at least 2 cycles of study treatment. The SMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

Then, on a periodic basis, approximately every 3 months from the date of the first-patient-in, the SMC will review safety data, including demographics, adverse events, serious adverse events, adverse events of special interest and relevant laboratory data.

4. STUDY OBJECTIVES

4.1. Primary objective

Primary objective of this study is to evaluate the efficacy of the addition of atezolizumab to FOLFOXIRI plus bev as first line treatment of patients with metastatic colorectal cancer in terms of Progression Free Survival (PFS).

4.2. Secondary objectives

Secondary objectives of this study are to evaluate the safety, activity and efficacy of the addition of atezoliumab to FOLFOXIRI plus bev in terms of:

- Overal toxicity rate
- Toxicity rate
- Objective response rate according to RECIST version 1.1 criteria (ORR)
- Immuno-related objective response rate according to modified RECIST criteria (irORR)
- Early Objective Response Rate (EOR)
- Deepness of response (DoR)
- R0 Resection Rate
- Progression Free Survival 2 (PFS2)
- 2nd-PFS
- Time to failure of strategy (TFS)
- Overall Survival (OS)
- Translational analyses including the evaluation of immunity-related parameters on samples collected both before and after the treatment.

5. PATIENTS' SELECTION

5.1. Inclusion criteria

- Written informed consent to study procedures and to molecular analyses
- 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 < or = 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 x 10^9/L, Platelets >100 x 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 x UNL (or <5 x UNL in case of liver metastases) alkaline phosphatase <2.5 x UNL (or <5 x UNL in case of liver metastases)
- Creatinine clearance ≥50 mL/min or serum creatinine 1.25 x UNL
- INR or aPTT ≤1.5 × ULN. Patients who are on therapeutic doses of anti-coagulants are eligible if they are on a stable dose of anti-coagulant for 28 days with stable INR and PTT values.
- 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
- Male subjects with female partners of childbearing potential must be willing to use adequate contraception as outlined in Section 5.5 – Contraception, starting

with the first dose of study therapy through 6 months after the last dose of bevacizumab and within 5 months after the last dose of atezolizumab.

- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject
- 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 continuous months, are surgically sterile, or are sexually inactive.
- Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.5 – Contraception, for the course of the study starting with the first dose of study therapy through 6 months after the last dose of bevacizumab and within 5 months after the last dose of atezolizumab.
- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject
- Will and ability to comply with the protocol

5.2. Exclusion criteria

- Radiotherapy to any site within 4 weeks before the study
- Previous adjuvant oxaliplatin-containing chemotherapy
- Previous treatment with bevacizumab
- Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
- Untreated brain metastases or spinal cord compression or primary brain tumours
- History or evidence upon physical examination of CNS disease unless adequately treated
- Hystory of haemoptysis ≥2 grade according to NCIC-CTG criteria within one month prior screening

- Active or untreated CNS metastases. Patients with a history of treated asymptomatic CNS metastases are eligible provided they meet all the following criteria:
    - ✓ Measurable disease outside the CNS
    - ✓ Only supratentorial or cerebellar metastases allowed (i.e. no metastases to midbrain, pons, medulla or spinal cord)
    - ✓ No ongoing requirement for corticosteroid therapy for CNS disease
- 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 histor 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.
- Active infection requiring antibiotics at the time of initiation of study treatment.
- Any previous venous thromboembolism ≥ NCI CTCAE Grade 4 .
- 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
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to initiation of study treatment
- 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 during the study and until 6 months after the last dose of bevacizumab and until 5 months after the last dose of atezolizumab..
- History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    - ✓ Note: History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
    - ✓ Note: Controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan
    - ✓ Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted
- Positive test for human immunodeficiency virus (HIV)

- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C
    - ✓ Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
    - ✓ Note: Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Prior allogenic bone marrow transplantation or solid organ transplant
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to start of study treatment, or requirement for systemic immunosuppressive medications during the trial. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
    - ✓ Note: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study.
- Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the atezolizumab formulation
- Administration of a live, attenuated vaccine within 4 weeks prior to start of study treatment or anticipation that such a live attenuated vaccine will be required during the study
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study treatment
- If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

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;
- Consent withdrawal

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.

5.5 Contraception

Bevacizumab, Atezolizumab and FOLFOXIRI (irinotecan + 5-FU + leucovorin, oxaliplatin), may have adverse effects on pregnancy and poses a risk to the human

fetus, including embryo-lethality. Furthermore, it is not known if these therapies have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Subjects should start using birth control from study screening visit throughout the study period until 6 months after the last dose of bevacizumab and until 5 months after the last dose of atezolizumab.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order

to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 12.7 - Pregnancies reporting procedure. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

6. PARTICIPATING CENTERS, ENROLLMENT AND STUDY TIMELINE

The AtezoTRIBE study will be initially conducted at the Coordinating Center (Department of Medical Oncology, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa) until 6 patients are randomly assigned to arm B. At that time, the enrollment of new patients will be temporary interrupted. When 6 patients enrolled in arm B receive at least 2 cycles of study treatment, a Safety Monitoring Committee (SMC) will complete a safety evaluation.

The enrollment will then resume and involve approximately 28 additional centers, only if the study treatment combination is judged feasible and no major safety concerns arise. A total of 201 patients will be enrolled.

The registration and randomization procedures will be centralized at Clinical Trials Coordinating Center - Istituto Toscano 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 1:2 ratio. Eligible patients will be stratified according to ECOG PS (0 *vs* 1, 2), primary tumor location (right *vs* left/rectum) and previous adjuvant chemotherapy (yes *vs* no).

The randomization will be performed by using an electronic WEB-based system according to the minimization algorithm.

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 30 months since the enrollment is expected to be about 12 months, 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: June 2018
2. First Patient In: Dec 2018
3. Safety run in data review: Apr 2019
4. Enrollment rate after safety run in: 25 pts/month
5. Last Patient In: Dec 2019
6. Last Patient Last Visit: Jun 2021
7. First data release PFS: Apr 2021
8. Manuscript submission: Oct 2021

7. STUDY TREATMENT AND PROCEDURES

7.1. Study treatment

Eligible patients will be randomized to receive:

Arm A:

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, followed by
- Irinotecan 165 mg/sqm iv over 60 minutes day 1, followed by
- Oxaliplatin 85 mg/sqm iv over 2 hours day 1, in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours day 1, followed by
- 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-FU is interrupted because of adverse events, patient's refusal or investigator's choice.

Arm B:

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

- Atezolizumab 840 mg iv over 30 minutes (60 minutes at the first infusion) day 1, followed by
- Bevacizumab 5 mg/kg iv over 30 minutes day 1, followed by
- Irinotecan 165 mg/sqm iv over 60 minutes day 1, followed by
- Oxaliplatin 85 mg/sqm iv over 2 hours day 1, in two-way with
- L-Leucovorin 200 mg/sqm iv over 2 hours day 1, followed by
- 5-fluorouracil 3200 mg/sqm 48 h-continuous infusion, starting on day 1

The dose of 840 mg atezolizumab administered every 2 weeks has the equivalent dose exposure as the 1200 mg every 3 weeks, the recommended dose of atezolizumab [69]. The atezolizumab dosage adopted is that commonly used when the drug is combined with agents with biweekly schedule (14– or 28-day cycle) [50-54]. With regard to FOLFOXIRI plus bev, no such toxicities will be expected to reduce doses when it is associated with immunotherapy.

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

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

In both arms, if disease progression does not occur during induction with FOLFOXIRI plus bev +/- atezolizumab, at the treating physician's discretion, the reintroduction after progression of the same induction treatment (up to 8 cycles) according to randomization arm, followed by maintenance until disease progression, unacceptable toxicity or patient's refusal, is recommended.

In the case of persistent neurotoxicity ≥ G2, FOLFIRI plus bev +/- atezolizumab will be administered for a maximum of 8 cycles.

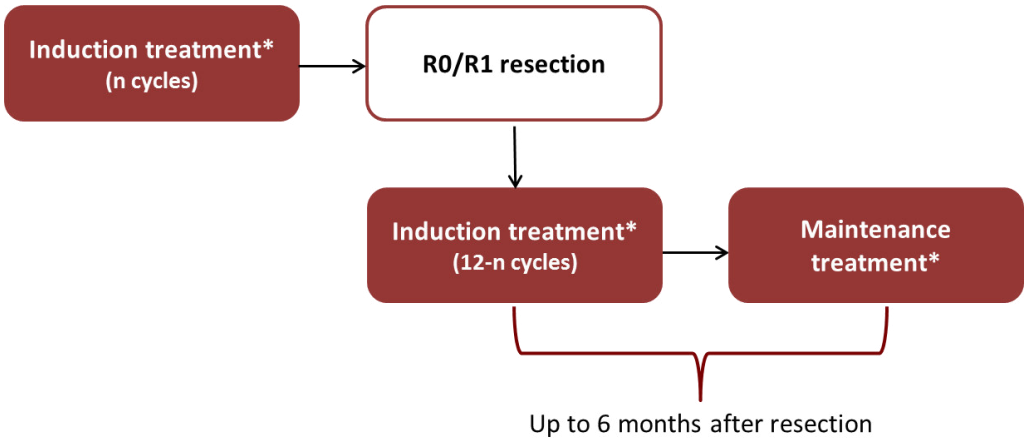
If no progression occurs after re-introduction of FOLFOXIRI plus bev +/- atezolizumab, patients will receive maintenance 5-FU/LV plus bev +/- atezolizumab at the same dose used in the last cycle of the induction treatment. 5-FU/LV plus bev +/- atezolizumab will be repeated biweekly until disease progression,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

The prosecution of bev +/- atezolizumab until disease progression is recommended also in the case of interruption of 5-FU 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 (pre- and post-resection) of the same induction regimen received before resection followed by maintenance up to a total of 12 post-operative cycles (including induction and maintenance) according to randomized arm. 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

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), TSH, fT3, fT4, amylase, lipase, International normalized ratio (INR)/Activated partial Thromboplastin Time (APTT), CEA, CA19.9; pregnancy test (if clinically indicate);
- Urinanalysis;
- Blood pregnancy test (only for women of childbearing potential);
- 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 immunohystochemistry and 10 slides 8 μm-thick;
- Collection of blood, plasma and feces 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), AST, ALT, 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);
- Collection of blood and plasma samples, only at the time of second cycle of first induction treatment (2nd cycle)

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), TSH, fT3, fT4, amylase, lipase, 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, only at the end of the first induction treatment (End Ind1), and at the time of first (PD1) and second (PD2) evidence of disease progression;
- Collection of feces samples, only at the end of the first induction treatment (V2) and at the time of the first evidence of disease progression (V3).

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 immunohystochemistry and 10 slides 8 μm-thick for molecular biology analyses, are required. Tissue samples will be collected also for tissue resected after treatment, when available. These specimens must be representative of both tumour core and invasive margin.

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 responsability of Dr. Cremolini.
Exploratory biomarker translational analyses, including but not limited to the evaluation of immunity-related parameters, on samples collected both before and after the treatment, will be performed in an effort to understand the association of these markers with study treatment outcome.

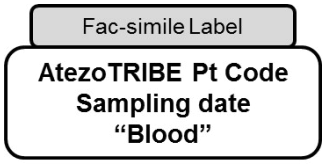
Eligible tissue samples including resections/biopsies of primary tumor and/or metastasis biopsies will be selected by the Foundation and prepared and shipped to HalioDx (Luminy Biotech Entreprises, 163 Avenue de Luminy - 13288 Marseille Cedex 9 FRANCE) in accordance with EC rules.

The tissue samples will be analysed to assess the role of the consensus Immunoscore in predicting the benefit from the addition of atezolizumab to first-line FOLFOXIRI/bev in mCRC patients.

A further essential point of this analysis will be the evaluation of the prognostic impact of the consensus Immunoscore classification in the CRC metastatic disease, and the assessment of the added value of the Halioseek test to better identify patients most likely to benefit from an Immuno Checkpoint Inibitor based therapeutic strategy.

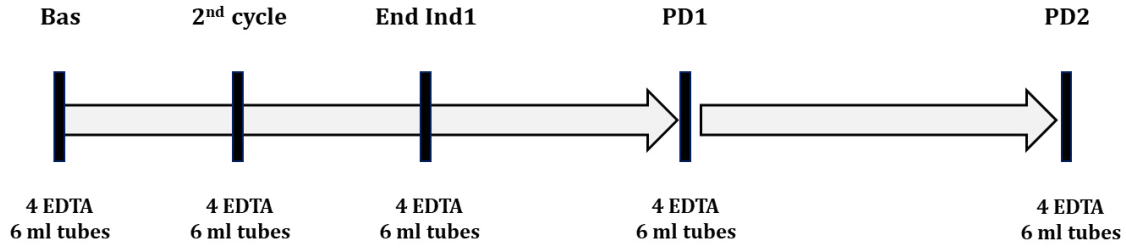
7.5. Blood sampling collection

Three 6ml EDTA tubes will be collected once at anytime before or during the treatment. They will be labelled as "AtezoTRIBE - Patient Code/ 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).



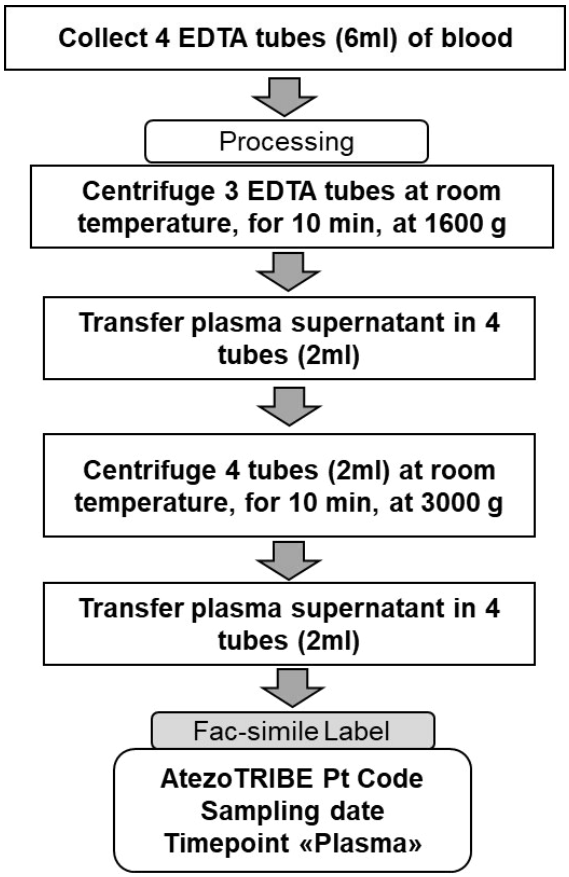
In addition, four 6 ml EDTA tubes will be collected at the following time-points:

- at baseline (Bas)
- at the second cycle (2nd cycle)
- at the end of first induction treatment (End Ind1)
- at the first evidence of PD (PD1)
- at the second evidence of PD (PD2)



These tubes will be centrifuged as soon as possible at room temperature at 1600 g for 10 minutes and plasma supernatant will be collected and divided into four aliquots, that will be centrifuged at room temperature at 3000 g for 10 minutes and plasma

supernatant will be collected in 4 tubes labelled as "AtezoTRIBE – Patient Code/ Date/ Bas or 2nd cycle or End Ind1 or PD1 or PD2/ Plasma " (see fac-simile) and will be stored at -80°C until shipment to the Coordinating Centre (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana).



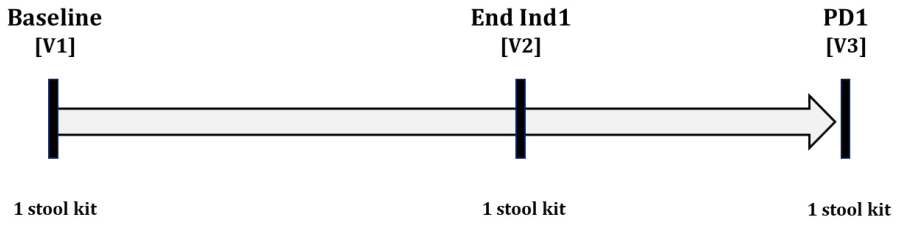
The shipment of blood samples will be arranged by the Fondazione GONO. that will provide dry ice for the shipment.

Blood- and plasma-derived biomarkers and their changes from baseline to subsequent clinically relevant timepoints during study treatment, including but not limited to biomarkers that are related to CRC or tumor immune biology, will be exploratory evaluated.

7.6. Collection feces

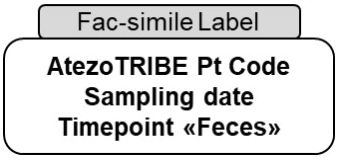
Samples of feces will be collected at the following time-points:

- at baseline (V1)
- at the end of first induction treatment (V2)
- at the first evidence of PD (V3).



Tum

Dedicated stool collection kits will be provided by GONO to all participating centers. Feces samples will be collected by patients at home, according to standardized procedures as described in each stool kit, labelled as "AtezoTRIBE - Patient Code/Date/V1 or V2 or V3/Feces" (see fac-simile). The samples will be frozen at the site (T= -80°C), until shipment to the Coordinating Center (U.O. Oncologia Medica 2 Universitaria – Azienda Ospedaliero-Universitaria Pisana).



A part of these samples will be selected by the Foundation and shipped to Gustave Roussy Cancer Campus (114,rue Édouard-Vaillant - 94805 Villejuif Cedex – France) in accordance with EC rules.

Feces-derived biomarkers and their changes from baseline to subsequent clinically relevant timepoints during study treatment, including but not limited to gut microbiota composition, will be exploratory evaluated .

7.7. Collection of CT scan images

Tumor response will be assessed throught contrast-enhanced chest and abdomen CT scans with a contiguous slice thickness of ≤ 7mm, 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 sybject 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.

7.8. Tabulated overview

Procedure	Screening (within 28 days before random)	Baseline	Before every cycle[1]	Every 8 wks [1]	After the 2nd evidence of PD
Informed Consent	X				
Complete medical history	X				
Inclusion/Exclusion Criteria Checked	X				
Tumor assessment (total-body CT or abdomen MRI + chest CT)	X			X	
Collection of a CD-ROM copy of CT scan	X			X	
12-lead ECG	X				
ECOG PS	X	X	X	X	
Physical examination	X		X	X	
Complete blood examination[2]	X			X	
Partial blood examination[3]		X	X		
Sierology[4]	X				
Dipstick proteinuria		X	X		
Blood pregnancy test	X[5]				
Collection of a paraffin-embedded tissue sample	X[6]				
Collection of blood samples		X	X[7]	X[8]	
Collection of feces samples		X		X[9]	
Adverse events and toxicity	X[10]	X	X	X	X[11]
Survival follow up					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), TSH, fT3, fT4, amylase, lipase, 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), AST, ALT, serum creatinine. INR/APTT only for patients on anticoagulation therapy;
4. HIV, HBC, HCV;
5. Only for women of childbearing potential;
6. Paraffin-embedded samples will be collected also for tissues resected after the treatment, when available;
7. Only at the second cycle;
8. Only at the end of first induction treatment, and at the first and second evidence of PD;
9. Only at the end of first induction treatment, and at the first evidence of PD;

10. AE assessment to be started after signing of IC until 90 days after last study treatment;
11. 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 CTCAE v5.0. 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 delays 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 encepalopathy)	Permanently discontinue

Hemorrhage	Any grade CNS	Permanently discontinue
	≥2 (pulmonary)	Permanently discontinue
	≥3 (non-pulmonary/non-CNS)	Permanently discontinue
Haemoptysis	≥2	Hold temporarily or 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
Nephrotic syndrome	Any grade	Permanently discontinue
GI perforation	Any grade	Permanently discontinue
PRES/RPLS	Any grade	Permanently discontinue
Major surgery	Any grade	Hold temporarily or permanently discontinue
Wound healing complications	Any grade	Hold temporarily or permanently discontinue
Fistula	Any grade TE fistula	Permanently discontinue
	≥2 (other than TE)	hold temporarily or permanently discontinue (at treating Investigator's discretion)
Febrile neutropenia/ thrombocytopenia	4	Hold temporarily

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. Addiction 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.
- ≥ 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: Discontinue bevacizumab treatment.

Thrombosis/Embolism

All toxicity will be graded according to CTCAE v5.0 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 ≥ 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

Dose delays for toxicities attributable to atezolizumab (dose reductions of atezolizumab are not permitted)

Adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Hepatitis	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue atezolizumab
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold atezolizumab *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving

Adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue atezolizumab
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Atezolizumab
Rash	Grade 3	Withhold Atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4	Permanently discontinue Atezolizumab
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue atezolizumab
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN)	Withhold atezolizumab

	or Grade 2 or 3 pancreatitis	Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab
Immune-related myositis	Grade 2 or 3	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per Day.
	Grade 4	Permanently discontinue atezolizumab

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology criteria for Adverse Event Version 5.0 (NCI-CTCAE v.5.).

Atezolizumab should be permanently discontinued:

- for Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones;
- for any recurrent event at Grade ≥ 3 severity;
- if a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date;
- if a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatment-related toxicity beyond 12 weeks after adverse reaction onset date.

Diarrhea

Patients who develop diarrhea of significant duration (> 5 days) or associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein or platelet count or bandemia), it is recommended to do the following:

• Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and

lymphocytic infiltrates in order to confirm colitis diagnosis. If possible, one or two biopsy specimens should be snap frozen and stored.

• Perform laboratory tests to rule out alternate etiology (i.e, WBCs and stool calprotectin).

Patients should be monitored for signs and symptoms of colitis.

Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients should be monitored for signs and symptoms of hepatitis. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other

causes for the increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti−smooth muscle antibody tests should be performed if an autoimmune etiology is considered.
Treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.
Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

Skin toxicity

Treatment-emergent rash has been associated with atezolizumab. The majority of the cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Endocrine Toxicity

Hypothyroidism, hyperthyroidism, diabetes mellitus type 1 and ipopituitarism have been associated with the administration of atezolizumab.
Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, endocrin pancreas, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be obtained to determine whether thyroid abnormalities are present; glicemia and insulinemia should be determined whether diabetes mellitus type 1 is suspected. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an antithyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis. Treatment with insulin should be initiated for type 1 diabetes

mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild to moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, or chronic obstructive pulmonary disease, or pulmonary hypertension:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (DLCO)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of other

immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workups should include an evaluation for obstruction, as well as serum amylase and lipase tests.

Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Pericardial Effusions

Pericardial involvement with associated effusions is common in patients with NSCLC and has the theoretical potential to be exacerbated by inflammation associated with anti-tumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with preexisting pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial effusions, appropriate workup includes cytology, LDH, glucose, cholesterol, and cell count. For patients with a pericardial

effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

Influenza-like illness

Influenza-like illness has been reported in patients receiving atezolizumab. Events associated with influenza-like illness were primarily observed one to two weeks after receiving the first cycle. Reactions have included fever, fatigue, asthenia, chills, myalgia, arthralgia and headache. The events have been mild to moderate in severity.

Neurologic disorders

Myasthenia gravis and Guillain-Barre syndrome have been observed in less than 1% of patients taking atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Meningitis (non-infectious) has also been reported in <1% of patients. Patients with meningitis may present with altered mental status, confusion, headache, or fever. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.

Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. Patients should be monitored for symptoms of motor and sensory neuropathy. Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2mg/kg/day of prednisone or equivalent) should be considered.

Hypersensitivity reactions

Hypersensitivity reactions including allergic and anaphylactic reactions have been reported in <1% of patients receiving single agent. Outcomes for these events were

considered resolved. Patients may present with complaints such as flushing, fever, chills, blood pressure change, tachycardia or shortness of breath.

Infusion-related reactions

Symptoms may present within 30 minutes to 24 hours after infusion, are generally mild and manageable, and wane with subsequent infusions. With single agent atezolizumab, infusion-related reactions (IRR) have been reported in 0.4% of patients. The most common symptoms reported with single agent use within 24 hours of the first cycle were pyrexia, fatigue, nausea, hypertension, headache and diarrhea.

The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Immune-related myositis

Immune-related myositis has been observed in less than 1% of patients taking atezolizumab as monotherapy. Patients may present with signs and symptoms of inflammatory muscle injury; dermatomyositis and polymiositis are among the most common disorders. Initial diagnosis in based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients should be closely monitored for signs and symptoms that are suggestive of immune-related myositis.

Treatment with atezolizumab should be withheld for ≥ Grade 2 myositis, and treatment with intravenous corticosteroids equivalent to 1 to 2 mg/kg/day methylprednisolone should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If corticosteroids are

initiated and myositis does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Treatment with atezolizumab may be resumed when myositis improves to ≤ Grade 1 within 12 weeks, or symptoms of myositis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent myositis.

For further information regarding management of atezolizumab-associated adverse events, please refer to the atezolizumab Investigator's Brochure.

8.2. Concomitant medications and management of specific adverse events

Acute colinergic 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

All patients should be premedicated prior to FOLFOXIRI administration to prevent emesis with:

- Dexamethasone 12 mg IV within 1 hour prior to infusion and dexamethasone 8 mg the day after the start of infusion;
- 5-HT3 antagonist (i.e. ondansetron 8 mg, granisetron 3 mg, palonosetron 0.25 mg) IV within 1 hour prior to infusion and the day after the start of infusion (except for palonosetron).

No antiemetic prophylaxis with corticosteroids is recommended during maintenance treatment.

Changes to the antiemetic prophylaxis are possible according to the center's guidelines. Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumor immune activity, it is recommended that dexamethasone doses should not be increased.

Allergic/Hypersensitivity reactions

Allergic/hypersensitivity reactions may occur during or following the administration of oxaliplatin. Prophylactic treatment with an antihistamine (i.e. clorfenamine 10 mg im/iv) is recommended.

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 treatment) 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 recommended dosage regimen for loperamide 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. The patient should also be instructed to notify the Investigator if diarrhea or abdominal cramps occur. If grade 2 diarrhea persists for more than 5 days despite loperamide, the patient should be instructed to take a budesonide, mesalamine or 10 mg oral prednisone equivalent per day and to re- contact the treating Investigator. In case of grade 3 or abdominal pain, blood or mucus in stool, the patient should be hospitalised for parenteral support, loperamide should be replaced by another anti-diarrheal treatment (e.g. octreotide) and administering prednisone 60 mg/day or equivalent. 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 irinotecan 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

According to the summary of product characteristics of each trial drugs, the following concomitant medications are prohibited during the study treatment:

- suxamethonium, ketoconazole, rifamcipin, carbamazepine, phenobarbital, phenyntoin, St. John's wort and atazanavir are not allowed in combination with Irinotecan;
- yellow fever vaccine should be avoided in patients receiving 5-FU and Irinotecan because of the potential for serious or fatal infections;
- clozapine, cimetidine, brivudine, sorivudine increase 5-FU side effects;
- Interactions with allopurinol have been observed with 5-FU, with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with 5-FU should be avoided.

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

Live attenuated vaccines are not allowed during treatment and within 5 months following the last dose of atezolizumab

Patients who are receiving denosumab prior to enrollment must be willing/eligible to receive a bisphosphonate instead while on study.

Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) is not allowed.

Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents) are not allowed except for inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency.

9. STATISTICAL METHODS

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

9.1. Primary endpoint

The primary endpoint is Progression Free Survival (PFS)

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.

9.2. Secondary endpoints

Secondary endpoints of this study are the following:

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 5.0), 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 5.0), during the induction and the maintenance phases of treatment.

Objective Response Rate (ORR) 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.

Immuno-related Objective Response Rate (irORR) is defined as the percentage of patients, relative to the total of enrolled subjects, achieving a complete (CR) or partial (PR) response, according to immune-modified RECIST 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 (EOR) is defined as the percentage of patients, relative to the total of the enrolled subjects, achieving a ≥ 20% decrease in the sum of diameters of RECIST target lesions at week 8 compared to baseline.

Deepness of Response (DoR) is defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir, in the absence of new lesions or progression of non-target lesions, when compared with 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.

Progression Free Survival 2 (PFS2) is defined as beginning with randomization and ending with the first of the following events: a) death; b) disease progression according to RECIST 1.1 criteria 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 metastasis will not result in censoring for PFS2. PFS2 will be analyzed both in the intention-to-treat population (whichever 2nd-line treatment will be adopted) and in the per-protocol population.

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 according to RECIST 1.1 criteria 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.

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.

9.3. Study populations for primary and secondary analyses

Modified intention to treat population (mITT)

The mITT population will include all patients who receive any amount of the study medication according to the randomization arm. The mITT 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 any amount of the study medication according to the treatment actually received. 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 FOLFOXIRI plus bev as first-line treatment and at least one cycle of 5-FU +/- oxaliplatin +/- irinotecan plus bev as second-line treatment (arm A) and at least one cycle of FOLFOXIRI plus bev plus atezolizumab as first-line treatment and at least one cycle of 5-FU +/- oxaliplatin +/- irinotecan plus bev plus atezolizumab as second-line treatment (arm B).

9.4. Analysis of endpoints

Analysis of primary endpoint

The primary analysis of PFS will be performed in the ITT population. The Kaplan-Meier approach will be used to estimate PFS and the 1-sided log-rank test will be adopted to compare study arms. A log-rank test stratified by the same factors as used for randomization will also be performed, as well as a multivariable model including all the significant baseline variables

Analysis of secondary endpoints

A one-sided log-rank test will be used to compare study arms in terms of PFS2, 2nd-PFS, TFS and OS. Hazard ratios and 1-sided 90 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 1-sided 90% 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 enrolled patients. The corresponding exact 1-sided 90% 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 enrolled 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 ¾ 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 PFS of each arm follows an exponential distribution and considering an expected median PFS of 12 months for standard arm[15], 129 events are required to detect a hazard ratio (HR) for PFS of 0.66 in favour of the experimental group (arm B), with a one-sided unstratified log-rank test, with α and β errors of 0.10 and 0.15, respectively [70]. Assuming an accrual rate of 210 subjects/year, a 1:2 randomization and a minimum follow up period equal to 1.5 years, a total of 201 patients should be randomized (arm A/B: 67/134).

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 and with the European Directive on the privacy of data (General Data Protection Regulation 2016/679).

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. Cremolini.

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 responsabilities

The Fondazione GONO 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 Fondazione GONO, 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 atezolizumab for all treatment, bevacizumab beyond progression 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 Responsabilities 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. SAFETY PARAMETERS AND DEFINITIONS

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 which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product." (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.

<u>Assessment of Causality of Adverse Events</u>

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments

• Known association of the event with the disease under study

• Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

• Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 1 will be used for assessing the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (Version 4.0), which can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

a: Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c: If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 12.3 for reporting instructions), per the definition of serious adverse event in Section 12.3.
d: Must be reported as serious adverse events (see Section 12.3 for reporting instructions), per the definition of serious adverse event in Section 12.3.
Deaths that are attributed by the investigator solely to progression of disease should be recorded only on the Study Discontinuation eCRF (see Section 12.6).

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 (Immediately Reportable to the Sponsor)

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 within 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first, and 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.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe or according to NCI CTCAE criteria; see Section 12.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF. Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event)

12.4 Adverse Events of Special Interest (AESI) to bevacizumab (Immediately Reportable to the Sponsor)

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 ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

12.5 Adverse Events of Special Interest (AESI) to atezolizumab (Immediately Reportable to the Sponsor)

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:

- Pneumonitis
- Colitis
- Endocrinopathies (Diabetes mellitus, Pancreatitis, Adrenal Insufficiency, Hyperthyroidism and Hypophysitis)
- Hepatitis
- LFTs abnormalities (AST/ALT ≥10 x ULN or AST/ALT ≥3 x ULN with total bilirubin >2 x ULN)
- 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:
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice
- Systemic Lupus Erythematosus

- Neurological disorders (Guillian-Barre Syndrome, Myasthenic syndrome or Myasthenia Gravis, and Meningoencephalitis)
- Nephritis
- Events suggestive of hypersensitivity, cytokine release syndrome, influenza like illness, SIRS (systemic inflammatory response syndrome), SIA (systemic inflammatory activation), infusion related reactions
- Vasculitis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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

a. *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).

12.6 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.
Deaths that are attributed by the investigator solely to progression of colorectal cancer should not be reported as a serious adverse event.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF.

12.7 Pregnancies reporting procedure

Pregnancy in Female patients

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.

A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), by scanning and emailing the form using the email address provided to investigators.

The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will update the Pregnancy Report eCRF when updated information on the course and outcome of the pregnancy becomes available.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study.

A Clinical Trial Pregnancy Reporting Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted to the sponsor.

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.

12.8 Methods and timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the Adverse Event eCRF. For each adverse event, the investigator will make an assessment of seriousness (see Section 12.3 for seriousness criteria), severity and causality (see Section 12.1) on the Adverse Event eCRF.

12.8.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation** of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies; see Section 12.3 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug, or initiation of new anti-cancer therapy, whichever occurs first.

After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug

12.8.2 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF; colloquialisms and abbreviations should be avoided. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

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.

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.

12.8.3 Adverse Events Associated with an Overdose or Error in Drug Administration

Study drug overdose is the accidental or intentional use of the drug(s) in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event but it may result in an adverse event. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF and reported as a protocol deviation. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills

seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

13. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 12.3 for further details)
- Non-serious adverse events of special interest (see Section 12.4, Section 12.5 for further details)
- Pregnancies (see Section 12.7 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

14. FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

14.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better or is assessed as stable by the investigator or until the patient is lost to follow-up or withdraws consent. Every effort should be made to follow all serious adverse events considered related to study drug or study-related procedures until a final outcome can be reported. During the study period, resolution

of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF. All pregnancies reported during the study should be followed until pregnancy outcome.

14.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

15. 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:
atezotribe@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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APPENDIX I

RECIST CRITERIA 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

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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 ≥ 10mm 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.

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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.

Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.
Modified Response Evaluation Criteria in Solid Tumors (mRECIST) is derived from RECIST version 1.1 (v1.1) conventions and immune-related response criteria (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

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Modified RECIST and RECIST v1.1: Summary of Changes		
	RECIST v 1.1	**mRECIST**
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

APPENDIX II

NCI Common Terminology Criteria for Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 5.0 for toxicity and serious adverse event reporting. A copy of the CTC Version 5.0 can be downloaded from the CTEP home page:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdfAll appropriate treatment areas should have access to a copy of the CTC Version 5.0.