KURZPROTOKOLL
MO29112

Öffentlicher Titel	Biomarker-gesteuerte Therapie bei metastasiertem Kolorektalkarzinom
Wissenschaftl. Titel	A Multi-centre Randomised Clinical Trial of Biomarker-driven Maintenance Treatment for First-line Metastatic Colorectal Cancer (MODUL)
Kurztitel	MO29112
Studienart	multizentrisch, prospektiv, randomisiert, offen/unverblindet, mehrarmig
Studienphase	Phase II
Erkrankung	Verdauung: Darmkrebs (Kolorektales Karzinom): Erstlinie
Einschlusskriterien	- All Cohorts - 1. Have provided written informed consent prior to any study specific procedures - 2. Willing and able to comply with the protocol - 3. >= 18 years of age - 4. ECOG status of <= 2 (see Appendix 5) - 5. At least 16 weeks of life expectancy at time of entry into the study - Disease-related - 6. Histologically confirmed mCRC - 7. Measureable, unresectable disease according to RECIST 1.1 - 8. No prior chemotherapy for CRC in the metastatic setting - 9. Archival tumour formalin-fixed paraffin-embedded tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis is available for submission to the Sponsor’s designated laboratory If the tumour block is not available, >= 20 slides cut within two weeks of shipping to the designated Laboratory will be accepted as an alternative (see Appendix 12).
Ausschlusskriterien	- All Cohorts; Other Prior or Current Treatments - 1. Less than 6 months from completion of any prior adjuvant chemotherapy or radiotherapy Bevacizumab — F. Hoffmann-La Roche Ltd Protocol MO29112, Version 3 67 - 2. Prior or current treatment with bevacizumab or any other anti-angiogenic drug (i.e. VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors) - 3. Current or recent (within 10 days of start of induction treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), therapeutic oral or parenteral anticoagulants, or thrombolytic agents for therapeutic purposes Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalised ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment. Prophylactic use of anticoagulants is allowed. - 4. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications - 5. Treatment with any other investigational agent within 28 days or 25 investigational agent half-lives (whichever is longer) prior to the start of study induction treatment Haematological, Biochemical and Organ Function - 6. Inadequate haematological function indicated by all of the following: •Absolute neutrophil count (ANC) < 1.5 x 109/L •Platelet count < 100 x 109/L •Haemoglobin < 9 g/dL (patients may have transfusions and/or growth factors to attain adequate haemoglobin)

- 7. Inadequate liver function indicated by all of the following: •Total bilirubin >= 1.5 x upper limit of normal (ULN) •Aspartate transaminase (AST) and alanine aminotransferase (ALT) >= 2.5 x ULN (>= 5 x ULN in patients with known liver metastases) •Alkaline phosphatase (ALP) 2 x ULN (5 x ULN in patients with known liver metastases)
- 8. Inadequate renal function indicated by all of the following: •Serum creatinine > 1.25 x ULN or calculated creatinine clearance < 50 ml/min •Urine dipstick for proteinuria >= 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
- 9. INR > 1.5 and aPTT > 1.5 x ULN within 7 days prior to start of study induction treatment for patients not receiving anti-coagulation therapy. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the Bevacizumab — F. Hoffmann-La Roche Ltd Protocol MO29112, Version 3 68 enrolling institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment General Criteria
- 10. Active infection requiring intravenous antibiotics at the start of study induction treatment
- 11. Previous or concurrent malignancy, except for adequately treated basal or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for five years prior to study entry
- 12. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
- 13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
- 14. Prior history of hypertensive crisis or hypertensive encephalopathy
- 15. Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents <= 6 months prior to start of study induction treatment, myocardial infarction <= 6 months prior to study enrolment, unstable angina, New York Heart Association (NYHA) Functional Classification Grade 2 or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment
- 16. History or evidence upon physical or neurological examination of central nervous system (CNS) disease (e.g. seizures) unrelated to cancer unless adequately treated with standard medical therapy
- 17. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of start of study induction treatment
- 18. Any previous venous thromboembolism > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within the last 12 months prior to start of study induction treatment
- 19. Active or untreated CNS metastases. Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks prior to start of study induction treatment
- 20. History of haemoptysis >= Grade 2 (defined as >= 2.5 mL bright red blood per episode) within 1 month of start of study induction treatment
- 21. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)

- 22. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to start of study induction treatment, or anticipation of need for major surgical procedure during the course of the study. Bevacizumab — F. Hoffmann-La Roche Ltd Protocol MO29112, Version 3 69
- 23. Minor surgical procedure including placement of a vascular access device, within 2 days of start of study induction treatment
- 24. History of abdominal fistula, gastrointestinal (GI) perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to start of study induction treatment
- 25. Serious, non-healing wound, active ulcer, or untreated bone fracture
- 26. Known hypersensitivity to any component of bevacizumab or any of the study medications
- 27. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- 28. Known dihydropyrimidine dehydrogenase (DPD) deficiency
- 29. Pregnancy or lactation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment
- 30. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, hormonal implants, combined oral contraceptives, vasectomised partner), during both the Induction and Maintenance Treatment Phases and for at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the MODUL trial participant and that the vasectomised partner has received medical assessment of the surgical success. Some of the study-related medication, such as vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolized by CYP3A4.In these cases, the use of an alternate highly effective method of contraception must be considered.
- 31. For men: refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1 % per year such as vasectomy, sexual abstinence or female partner use of hormonal implants or combined oral contraceptives) during both the Induction and Maintenance Treatment Phases and for a period of at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with either, cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the Bevacizumab — F. Hoffmann-La Roche Ltd Protocol MO29112, Version 3 70 patient ensures compliance. A vasectomised MODUL trial participant is a highly effective birth control method provided that the MODUL trial participant has received medical assessment of the surgical success.
- Cohort-Specific Exclusion Criteria Cohort 1 – BRAFmut Exclusion Criteria
- 1. Inability to swallow pills

- 2. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption
- 3. History or presence of clinically significant ventricular or atrial dysrhythmias >= NCI CTCAE Grade 2
- 4. Corrected QT (QTc) interval >= 480 msec at Baseline or history of congenital long QT syndrome or uncorrectable electrolyte abnormalities
- 5. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use an alternate highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, vasectomised partner) other than hormonal contraceptives, during both the Induction and Maintenance Treatment Phases and for at least 6 months after the last dose of study medication. Vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolized by CYP3A4,
- Cohort 2 – No Biomarker Exclusion Criteria
- 1. 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 metastases allowed (i.e. no metastases to midbrain, pons, cerebellum, medulla or spinal cord)
- 2. Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the anti-PD-L1 antibody formulation
- 3. 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 (see Appendix 6 for a more comprehensive list of autoimmune diseases) Note: History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this cohort. Bevacizumab — F. Hoffmann-La Roche Ltd Protocol MO29112, Version 3 71 Note: Controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this cohort.
- 4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- 5. 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 imaging Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- 6. Positive test for human immunodeficiency virus (HIV)
- 7. 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 antibody test) are eligible. Note: Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction testing is negative for HCV ribonucleic acid (RNA).
- 8. Active tuberculosis
- 9. Administration of a live, attenuated vaccine within four weeks prior to start of maintenance treatment or anticipation that such a live attenuated vaccine will be required during the remainder of the study
- 10. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents

- 11. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within four weeks or five half-lives of the drug, whichever is shorter, prior to start of maintenance treatment
- 12. 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 agents) within 2 weeks prior to start of maintenance treatment, or requirement for systemic immunosuppressive medications during the remainder of the study. 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 after discussion with and approval by the Medical Monitor.

Alter	18 Jahre und älter
Fallzahl	1442
Prüfzentren	**Krankenhaus Nordwest GmbH** (Rekrutierung beendet) Institut für klinisch-onkologische Forschung Steinbacher Hohl 2-26 60488 Frankfurt am Main Prof. Dr. med. Salah-Eddin Al-Batran Tel: 069 7601 4420 albatran@khnw.de
Sponsor	Roche Pharma AG
Förderer	Roche Pharma AG
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02291289 EudraCT 2014-001017-61