STUDY TYPE	Phase-II, open-label, prospective, multicenter study
PRINCIPAL INVESTIGATOR	Prof. Dr. Stefan Kasper-Virchow Department of Medical Oncology West German Cancer Center, University Hospital Essen Hufelandstr. 55 45147 Essen Tel: +49 201 723 3449, FAX: +49 201 723 5549 E-Mail: stefan.kasper@uk-essen.de
SPONSOR	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin Phone: +49 30 814 534 431; Fax: +49 30 322 932 926 E-Mail: info@aio-studien-ggmbh.de
CONDITION	colorectal cancer
DESIGN	Main study: Single-arm, open label, phase II study Sub-study: Single-arm, open label, exploratory phase II study
INDICATION	Patients with MSI-high or MMR-deficient stage III colorectal cancer who are ineligible for oxaliplatin-based adjuvant chemotherapy or who refuse to receive an oxaliplatin-based adjuvant chemotherapy. For the main study, patients must have undergone R0 tumor resection. For the sub-study, R0 tumor resection must be planned.
PRIMARY OBJECTIVES MAIN STUDY	To determine if atezolizumab can significantly improve disease-free survival rate at 3 years compared to historical control when used as adjuvant treatment in patients with MSI-H/dMMR stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option.
SECONDARY OBJECTIVES MAIN STUDY	To determine if atezolizumab shows promising efficacy (DFS and OS) compared to historical control when used as adjuvant treatment in patients with MSI-H/dMMR stage III colon or rectal cancer for whom oxaliplatin regimens are not a viable treatment option. To assess the safety and tolerability profile of atezolizumab in patients with MSI-high stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option

	To determine the impact of atezolizumab on patient-reported outcomes and health-related QoL, and functional domains of health-related QoL.
EXPLORATORY OBJECTIVES MAIN STUDY	To estimate the ctDNA-free rate defined as the proportion of patients without detectable ctDNA after 12 months of adjuvant treatment. To explore the biologic activity of study treatment in terms of biomarkers in liquid biopsies, immune-related biomarkers and gene expression in peripheral blood mononuclear cells, the role of the gut microbiome in immunotherapy, as well as the predictive value of tumor mutational burden for response to immunotherapy.
SUB-STUDY OBJECTIVES	Primary objective: To assess the efficacy of perioperative atezolizumab in patients with MSI-high clinical stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option in terms of pathological complete (pCR) or subtotal (<10% vital tumor cells) regression after 4 weeks of neoadjuvant treatment Secondary objectives: To asses efficacy in terms of disease-free survival and overall survival. To assess safety, tolerability, and QoL of perioperative in patients with MSI-high clinical stage III colorectal cancer for whom oxaliplatin regimens are not a viable treatment option. Exploratory objectives: To estimate the ctDNA-free rate defined as the proportion of patients without detectable ctDNA after 12 months of adjuvant treatment. To explore the biologic activity of study treatment in terms of biomarkers in liquid biopsies, immune-related biomarkers and gene expression in peripheral blood mononuclear cells, the role of the gut microbiome in immunotherapy, as well as the predictive value of tumor mutational burden for response to immunotherapy.
SCHEME OF THERAPY	Main study: ▪ Atezolizumab 840mg i.v., on Day 1 and Day 15 (q2w) of every 28-day treatment cycle for a total of 12 cycles (24 doses) Sub-study: ▪ **Neoadjuvant treatment:** Atezolizumab at 1200 mg i.v. on Day 28 before surgery ▪ Atezolizumab at 1200 mg i.v. on Day 7 before surgery **Adjuvant treatment:** is identical to the main study; to begin within 70 days after surgery and after adequate recovery of the patient.
STUDY RATIONALE	We hypothesize that atezolizumab will improve the prognosis of patients with stage III dMMR CRC ineligible for or refusing oxaliplatin-based

	adjuvant chemotherapy compared to SOC and that these could therefore be promising therapeutic options. The current standard of care for adjuvant treatment of oxaliplatin-ineligible patients with stage III dMMR colon cancer is fluoropyrimidine monotherapy. In the COLOPREDICT registry, the 3 years DFS rate for such patients >70 years of age is 63% (95%CI: 53-75%) (Reinacher-Schick, unpublished data). In contrast to patients with mismatch repair proficient (pMMR) colon cancer, however, it is not established whether patients with stage III dMMR colon cancer benefit from adjuvant fluoropyrimidine monotherapy at all. For patients with stage II colon cancer in an otherwise identical setting, there is no indication for adjuvant treatment due to a lack of clinical benefit compared to surgery alone. Clinical results suggests a similar situation for stage III malignancy. Similar to other checkpoint inhibitors (CPI), the PD-L1 antibody atezolizumab demonstrated impressive activity and good tolerability in patients with metastatic dMMR CRC. Recently, the randomized phase III Keynote-177 trial was presented. In Keynote-177, patients with dMMR metastatic CRC were randomized to the PD-1 antibody pembrolizumab or to chemotherapy (mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab as per Investigator`s choice). Pembrolizumab treatment resulted in a statistically significant prolongation of Progression-free survival (16.5 mo [95%CI 5.4-32.4 mo] vs. 8.2 mo [95%CI 6.1-10.2 mo]; HR=0.60 [95%CI 0.45-0.80]; p=0.0002) and higher objective response rate (43.8% [95%CI 35.8-52.0%] vs. 33.1% [95%CI 25.8-41.1%] along with a markedly longer duration of response (duration of ≥ 24 mo in 82.6% vs. 35.3%). In addition, side effects were lower with pembrolizumab and quality of life was improved compared to conventional chemotherapy. Thus, pembrolizumab will become the new standard of care in patients with dMMR metastatic CRC in first-line therapy. Preoperative short-term administration of a combination of CPIs in MSI-high colorectal cancers has induced high rates of pathological regression in a recently presented small explorative phase II study. Six weeks of preoperative administration of the CTLA-4 antibody ipilimumab and the PD-1 antibody nivolumab resulted in a 100% complete or subtotal pathological remission in 7 patients with early-stage (I to III) mismatch repair deficient colon cancer. Therefore atezolizumab could be a promising strategy especially in MSI-high CRC patients who are not candidates for extensive surgery.
INCLUSION CRITERIA	1. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations 2. Male or female ≥ 18 years of age

	3. Histologically confirmed adenocarcinoma of the colon or rectum 4. For the main study: Pathological Stage III disease For the perioperative sub-study: Clinical stage III disease 5. For the main study: R0-resected primary tumor For the perioperative sub-study: Resectable primary tumor; R0 resection anticipated (R1-resected patients can remain on study.) 6. Tumor is MSI-high (MSI-H) or MMR-deficient (dMMR) For the main study: assessed from biopsy or from resected tumor tissue For the perioperative sub-study: assessed from biopsy 7. ECOG status 0 – 2 8. Ineligible for oxaliplatin-based adjuvant chemotherapy or patient's refusal of oxaliplatin-based adjuvant chemotherapy. Oxaliplatin ineligibility criteria are upon other: ▪ Age ≥70 ▪ Peripheral sensory neuropathy > grade 1 ▪ QT interval prolongation or co-medication with drugs known to prolong the QT interval ▪ Renal impairment (glomerular filtration rate <60ml per min) ▪ Suboptimal controlled diabetes mellitus (HbA1C>6,5%) with the risk of aggravation upon corticoid premedication for oxaliplatin based chemotherapy ▪ other criteria that the investigator consider as contraindications against oxaliplatin 9. Adequate blood count, liver enzymes, and renal function – re-testing can be undergone once in case of initial results near cutoff ▪ White blood cell count ≥ 3.5 x 10^6/mL ▪ Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3) ▪ Hemoglobin ≥9 g/dL (blood transfusion >2 weeks before testing is permitted) ▪ AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal ▪ Serum Creatinine ≤ 1.5 x institutional ULN and a calculated glomerular filtration rate ≥ 30 mL per minute 10. Patients not receiving therapeutic anticoagulation must have an INR < 1.5 ULN and PTT < 1.5 ULN within 7 days prior toregistration. The use of full dose anticoagulants is allowed as long as the INR or PTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose for anticoagulants for at least three weeks at the time of registration. 11. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

	12. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly-effective contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of study drug.
EXCLUSION CRITERIA	1. Severe infection within 4 weeks prior to registration, including, but not limited to, hospitalization for complications of infection, bacteremia, known active pulmonary disease with hypoxia, or severe pneumonia or any active infection (bacterial, viral or fungal) requiring systemic therapy within 4 weeks prior to registration . Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study. Patients with positive test result for SARS-CoV2 should be managed as per local institutional guidelines. 2. For the main study: Distant metastases or residual disease For the perioperative sub-study: Distant metastases or macroscopic residual disease (R2 resection status) 3. Neoadjuvant radiotherapy or radio-chemotherapy (enrollment of rectal cancer patients without prior radio- or radio-chemotherapy is allowed); prior neoadjuvant radio-chemotherapy (RCT) or radiotherapy (RT) for rectal cancer is allowed if >5 years and secondary colorectal cancer 4. Prior adjuvant chemotherapy for colorectal cancer; allowed if >5 years and secondary colorectal cancer 5. Prior treatment with atezolizumab or any other checkpoint inhibitor (anti-PD-1, anti-PD-L1, anti CTLA-4) 6. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to treatment start, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions: Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible. Inhaled corticosteroids for chronic obstructive pulmonary disease or bronchial asthma, supplemental mineralo-corticosteroids or low-dose corticosteroids for adrenal-cortical insufficiency are allowed 7. Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment. 8. History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins.

	9. Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation. 10. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. If any of these lung diseases is suspected based on the patient's history or the integrated evaluation of clinical and radiological records, an additional spirometry should be conducted. 11. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening followed by a negative HBV DNA test, are eligible for the study. The HBV DNA test will be performed only for patients who have a positive total HBcAb test. Patients are also eligible if HBV DNA < 500 IU/mL obtained within 28 days prior to initiation of study treatment, AND anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study. 12. Anti-viral therapy against HCV during the trial (but allowed prior to trial) 13. Positive human immunodeficiency virus (HIV) test. As an exception, known HIV+ patients may be included if they have: ▪ A stable regimen of highly active anti-retroviral therapy (HAART) ▪ No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections ▪ A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests 14. a) Treatment with a live, attenuated vaccine within 4 weeks prior to first dose of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the last dose of study treatment. b) Treatment with any vaccine during screening and the first cycle of treatment. 15. Active tuberculosis (as ruled out by clinical evaluation including medical history, physical examination, radiographic findings on baseline CT/ MRI of chest/abdomen/pelvis; if active tuberculosis is suspected, tuberculosis testing should be performed as per local standard of care). 16. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis,

	inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis. The following exceptions apply: ▪ Patients with a history of autoimmune-mediated hypothyroidism who are on thyroid replacement hormone are eligible for the study. ▪ Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. ▪ Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (i.e., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: ▪ Rash must cover < 10% of body surface area ▪ Disease is well controlled at baseline and requires only low-potency topical corticosteroids ▪ No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months 17. Prior (<3 years) or concurrent malignancy that either progresses or requires active treatment. Exceptions are: basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a or T1b prostate carcinoma, or superficial urinary bladder tumor [Ta, Tis and T1]. Patients with concurrent localized colorectal cancers, i.e. in case of HNPCC are eligible as far as all cancers are MSI^{high} or dMMR and tumors are resectable (for sub-study) or has been R0 resected (for adjuvant main study). 18. History of allergic reaction to any mycobacterial product 19. Prior allogeneic stem cell or solid organ transplantation requiring immunosuppressive therapy or other major immunosuppressive therapy 20. Severe non-healing wounds, ulcers or bone fractions 21. Evidence of bleeding diathesis or coagulopathy 22. Major gastrointestinal bleeding within 4 weeks prior to treatment start, unless cause of bleeding was the resected tumor. 23. Major surgical procedures other than primary tumor resection, except open biopsy, nor significant traumatic injury within 28 days prior toregistration, or anticipation of the need for major surgical procedure during the course of the study except for surgery of central intravenous line placement for chemotherapy administration. 24. Medication that is known to interfere with any of the agents applied in the trial. 25. Female subjects who are pregnant or breast-feeding; male or female patients of reproductive potential who are not employing an effective

	method of birth control as listed in the protocol. Women of childbearing potential must have a negative pregnancy test. 26. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or affect patient safety or study results 27. Participation in another clinical study with an investigational drug within 28 days prior to treatment start or 7 half-lives of previously used trial medication, whichever is longer 28. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities (AMG § 40, Abs. 1 No. 4) 29. Affected persons who might be dependent on the sponsor or the investigator
STATISTICAL ANALYSIS	In order to avoid treating an unacceptably high number of patients with an experimental regimen, a standard single stage design according to Fleming is applied in each randomized arm separately. The hypothesis test is conducted against historical control. In the COLOPREDICT registry, the 3-year DFS rate for patients >70 years with stage III dMMR tumors treated with adjuvant fluoropyrimidine therapy is 63% (95%CI: 53-75%) (Reinacher-Schick, unpublished data). The observed DFS rate of the COLOPREDICT registry will serve as historical control for a formal hypothesis test. Assuming a true DFS rate of 80% at 3 years, the study requires 46 subjects (in each arm) to decide whether the proportion surviving without disease relapse is less than or equal to 63% or greater than or equal to 80% with a one-sided significance level of 0.05 and power of 80%. If the number of responses is 35 or more, the hypothesis that H0 ≤ 0.63 is rejected with a target error rate of alpha=0.05. If the number of responses is 34 or less, the hypothesis that H0 ≤ 0.63 cannot be rejected. To facilitate a Per-Protocol analysis, the formal sample size is inflated by 8% to yield 50 patients per treatment arm as the accrual goal for the main study. The sample size for the exploratory sub-study was chosen on grounds of feasibility. The treatment is more experimental than the main study, therefore a smaller sample size is warranted. The pathological complete or subtotal regression in the sub-study will be evaluated exploratively. A complete or subtotal (<10% vital tumor cells) regression rate >30% will be considered as clinically meaningful to provide a rationale for further investigation of this strategy. With a sample size of n=20 patients it is possible to test a rate of complete or subtotal regression of 30% ± 13.5% with a 1-sided type I error of 10%. The final decision if the strategy will be regarded as successful will be made after calculating the respective confidence interval.

TRIAL DURATION	Q1/2022-Q4/2024; 2.5 years enrollment, 1 year treatment LPI Q4/2024 LPLV Q4/2027
NUMBER OF PATIENTS	All arms will be independently compared to patients with MSI high CRC in the COLOPREDICT registry (both historic control and updated real-world data available at the time of primary analysis), which are only treated with a fluroropyrimidine or which received no adjuvant therapy. In addition 20 patients will be enrolled into a perioperative, explorative sub-study in 5 selected study centers. Patients with clinical stage III tumors assessed by CT or MRI in these selected centers will be asked to be enrolled into the perioperative sub-study. A total of 80 patients will be enrolled (50 in arm A, 10 in arm B (which is already closed) and 20 patients in an explorative perioperative sub-study). Stratification T stage: (T1-3/N1 vs. (T4 and/or N2); Left-sided vs. right-sided. In the explorative sub-study 20 patients with clinical stage III disease based on a preoperative CT or MRI scans will receive neo-adjuvant atezolizumab for 4 weeks. After resection these patients will receive the adjuvant therapy with atezolizumab for additional 12 months.