Synopsis

Sponsor	AIO-Studien-gGmbH
Sponsor Signatory	Dr. Mischo Kursar
Investigational Product	Aflibercept (ZALTRAP®)
Study Title	mFOLFOX6 vs. mFOLFOX6 + aflibercept as neoadjuvant treatment in MRI-defined T3-rectal cancer: a randomized phase-II-trial
Trial sites / Investigators	**German sites:** • Universitätsmedizin Mannheim, Interdisziplinäres Tumorzentrum, Theodor-Kutzer-Ufer 1 – 3, 68167 Mannheim/ Prof. Dr. med. Ralf-Dieter Hofheinz (LKP) • Krankenhaus Nordwest GmbH, Institut für klinisch-onkologische Forschung, Steinbacher Hohl 2-.26, 60488 Frankfurt/ Prof. Dr. S.-E. Al-Batran • Universitätsklinikum Ulm, Klinik für Innere Medizin I, Albert-Einstein-Allee 23, 89081 Ulm/ Dr. Thomas Ettrich • Kliniken Maria Hilf GmbH, Krankenhaus St. Franziskus, Medizinische Klinik I, Viersener Str. 450, 41063 Mönchengladbach/ Prof. Dr. Ullrich Graeven • Klinikum Weiden, Med. Klinik I, Söllnerstr. 16, 92637 Weiden/ Dr. Alaa Eddin Harba, Dr Martina Troppmann • Praxis für Innere Medizin, Chausseestr. 42, 13357 10115 Berlin/ Prof. Dr. Andreas Josting • St. Vincenz-Krankenhaus Paderborn, Med. Klinik I, Am Busdorf 2, 33098 Paderborn/ Prof. Jobst Greeve • Klinikum Bogenhausen, Interdisziplinäre Onkologische Tagesklinik, Englschalkiner Str. 77, 81925 München/ Dr. Martin Fuchs • Praxis Dr. Vehling-Kaiser, Ländgasse 132-135, 84028 Landshut/ Dr. Ursula Vehling-Kaiser • Gesundheitszentrum St. Marien GmbH, Mariahilfbergweg 7, 92224 Amberg/ Dr. Ludwig Fischer von Weikersthal • Caritasklinikum Saarbrücken, St. Theresia, Klinik für Hämatologie und Onkologie, Rheinstr. 2, 66113 Saarbrücken/ Prof. Dr. Michael Clemens • HELIOS Klinikum Bad Saarow, Klinik für Hämatologie, Onkologie und Palliativmedizin, Pieskowerstr. 33, 15526 Bad Saarow/ Dr. Daniel Pink • Krankenhaus der Barmherzigen Brüder, I. Med. Abteilung, Nordallee 1, 54292 Trier/ Dr. Heinz Kirchen • MVZ Mitte, Onkologische Schwerpunktpraxis, Johannisplatz 1, 04103 Leipzig/ Dr Bärbel Schädlich, Dr. Albrecht Kretzschmar • Klinikum Wolfsburg, II. Med. Klinik, Sauerbruchstr. 7, 38440 Wolfsburg/ Prof. Dr. Nils Homann • Prosper-Hospital, Med. Klinik I, Mühlenstr. 27, 45659 Recklinghausen/ Prof. Thomas Höhler • Klinikum Magdeburg gGmbh, Klinik für Hämatologie/ Onkologie, Birkenallee 34, 39130 Magdeburg/ Dr. Kersten Borchert, PD Dr. Christoph Kahl • Krebsheilkunde Lichtenberg, Landsberger Allee 277a, 13055 Berlin/ Dr. Reinhard Musch • Leopoldina-Krankenhaus der Stadt Schweinfurt GmbH, Medizinische Klinik I, Gustav-Adolf-Str. 8, 97422 Schweinfurt/ Prof. Dr. med. Stephan Kanzler

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Publication (reference)	
Studied period	First patient enrolled: 24-JUL-2017 Last patient enrolled: 11-JAN-2021 Last patient completed: 01-JUN-2022

Objectives	**Primary objective** To investigate the efficacy of the mFOLFOX6/aflibercept combination compared to mFOLFOX6 alone in patients with locally advanced rectal cancer staged cT3 circumferential resection margin (CRM)-negative with MRI regarding the pathological tumor response based on central pathologic review. <u>Corresponding endpoint</u> • Pathological complete response (pCR) **Secondary objectives** To assess further efficacy and safety of the mFOLFOX6/aflibercept combination compared to mFOLFOX6 alone in patients with locally advanced rectal cancer staged cT3 CRM-negative with MRI <u>Corresponding endpoint</u> Efficacy • Disease-free survival (DFS) rate • Relapse-free survival (RFS) in resected patients • Overall survival (OS) • Rate of R0-wide, R0-narrow (according to CRM definitions in S3-guideline Version 1.1 August 2014), R1 and locoregional R2 resection • Downstaging and downsizing using a standardized regression grading (Dworak regression grading) Safety • Dose intensities of study medication • Type, incidence and severity of (serious) adverse events (AEs/SAEs) • Dose reduction or discontinuation of study drug due to AEs • Rate of treatment discontinuation due to toxicity • Type, incidence and severity of laboratory abnormalities • Vitals signs, physical examination, WHO/ECOG Surgical morbidity and mortality • Type, incidence and severity of perioperative medical events • Mortality within 28 days after surgery
Methodology	This was an open-label, randomized, multicenter, phase II study of mFOLFOX6 alone or in combination with aflibercept as neoadjuvant treatment in MRI-defined T3-rectal cancer. Eligible patients were randomized 1:2 in Arm A (mFOLFOX6 only) or Arm B (mFOLFOX6 plus aflibercept). Total mesorectal excision (TME) surgery was scheduled 4 weeks after the 6th cycle of treatment. After surgery, patients were treated at the discretion of the treating physician outside the study.
Number of patients (planned and analyzed):	Planned: Initial planned sample size: N=209 (70 in Arm A and 139 in Arm B) Analyzed: N=119 patients (N=39 patients in Arm A and N=80 patients in Arm B). In November 2019 patient number was reduced within a protocol amendment due to initial slow recruitment.
Diagnosis and main criteria for inclusion	Patients with locally advanced rectal or rectosigmoid cancer staged cT3 CRM-negative with MRI **Main criteria for inclusion** • Diagnosis of rectal adenocarcinoma

	• Candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy according to the primary surgeon, i.e. no patient will be included for whom surgeon indicates need for abdomino-perineal resection (APR) at baseline. • Clinical staging is based on the combination of the following assessments: – Physical examination by the primary surgeon – CT scan of the chest/abdomen – Pelvic MRI – Rigid rectoscopy / endoscopic ultrasound (ERUS). – Both examinations (MRI + ERUS) are mandatory. • The tumor has to fulfill the following criteria: – No symptomatic bowel obstruction – Locally advanced rectal and rectosigmoid cancer, i.e. lower border of tumor > 5 cm and < 16 cm from anal verge as determined by rigid rectoscopy – MRI criteria: a. Lower border of tumor below a line defined by promontorium and symphysis, regardless of the criterion "< 16 cm from anal verge as determined by rigid rectoscopy". b. No evidence that tumor is adjacent to (defined as within 2 mm of) the mesorectal fascia on MRI (i.e. CRM > 2 mm) c. Only T3-tumors are included, i.e. infiltration into perirectal fat < 10 mm provided CRM > 2 mm *Note:* MRI criteria are used for the definition of T3 tumor (i.e. exclusion of T2 and T4 situation).
Test product, dose and mode of administration, batch number	<u>Aflibercept:</u> • ZALTRAP® (aflibercept) has been given by i.v. infusion at a dose of 4 mg/kg on day 1 of a 14-day cycle (q2w) Aflibercept 100 mg (4 mL concentrate) Batch No. (expiry date): 02E2017: 05/2018 10E2017: 05/2018 05E2018: 03/2020 07E2018: 10/2020 10E2018: 10/2020 02E2019: 10/2020 04E2019: 10/2020 11E2019: 02/2021 01E2021: 08/2023 Aflibercept 200 mg (8 mL concentrate) Batch No. (expiry date): 02Z2017: 05/2018 10Z2017: 06/2018 05Z2018: 01/2020 07Z2018: 01/2020 08Z2018: 01/2020 10Z2018: 01/2020 02Z2019: 02/2020 04Z2019: 04/2020 05Z2019: 04/2020 11Z2019: 10/2020 06Z2020: 02/2021 10Z2020: 05/2021

	<u>mFOLFOX6</u> • Oxaliplatin 85 mg/m^2 i.v. on day 1 of a 14-day cycle (q2w) • Leucovorin 350 mg/m^2 i.v. as 2 h infusion on day 1 of a 14-day cycle (q2w) • 5-fluorouracil (5-FU) 400 mg/m^2 i.v. as bolus on day 1 and 2400 mg/m^2 as 46 h infusion (q2w) • Batch No.: Not applicable (medication not provided as IMP but standard use of products with marketing authorization).
Duration of treatment:	Patients received up to 6 cycles of mFOLFOX6 alone (Arm B) or 6 cycles of mFOLFOX6 in combination with 5 cycles of aflibercept (Arm B).
Efficacy evaluation criteria:	Tumor assessment by MRI was performed at screening to check the inclusion criteria and 3-4 weeks after the last administration of chemotherapy in order to rule out progression of the primary tumor and to enable salvage treatment (generally chemoradiotherapy) and to plan for surgery. Patients with clinical signs of tumor progression during the neoadjuvant treatment phase were treated individually according to tumor board decisions (recommended: chemoradiotherapy followed by TME surgery). Grading of the regression according to Dworak was performed after surgery and resected tumor specimens of the patients were assessed in a standardized manner independently by the central pathology. After end of treatment, patients were followed for survival and subsequent therapies for at least 12 but no more than 36 months after last patient last treatment or until death, lost to follow-up or withdrawal of consent, whichever occurred first.
Safety evaluation criteria	All patients who received at least one dose of study medication have been included in the safety analyses. Safety assessments consisted of monitoring and recording of all adverse events (AEs), including serious adverse events (SAE), from date of informed consent until date of end of treatment 4 weeks after surgery or until earlier termination. In case of earlier termination, safety follow-up was performed 4 weeks after last administration of study drug or before start of a subsequent anti-cancer treatment, whichever occurred first. Common terminology criteria for adverse events (CTCAE V 4.03) were used for grading.
Statistical methods:	Except for the primary endpoint, all parameters were evaluated in an explorative or descriptive manner, providing means, medians, interquartile and total ranges, standard deviations and/or confidence intervals, counts and proportions, or Kaplan-Meier curves, as appropriate for the respective data types. In general, all analyses were presented, and calculations performed based on the data actually available for each item (observed case analyses). Incomplete time-to-event observations were handled as censored measurements. No imputation of missing values were performed.
SUMMARY CONCLUSIONS **EFFICACY RESULTS:**	Pathological complete response is numerically lower with aflibercept combination compared to the chemotherapy alone. In addition, higher amounts of pN+ tumors were observed in Arm B. Furthermore, no differences were observed regarding DFS, RFS and OS. Thus, the combination of neoadjuvant chemotherapy with angiogenesis inhibition could not increase the efficacy compared to chemotherapy alone. However the very low rate of local recurrence and the long DFS in both arms (i) indicates good efficacy of radiotherapy free treatment and (ii) encourages further rectal cancer trials omitting radiotherapy by using the MRT based inclusion criteria established in the current trial.

SAFETY RESULTS:	The incidence of AEs was similar in both arms, however, the incidence adverse events with grade ≥ 3 (whether related or not) was more than twice as high for the combination with aflibercept. Two fatal SAEs were reported in Arm B with none of them related to the treatment. Surgical complications were similar in both arms, and especially no increase of anastomotic leak incidence was observed by the addition of the angiogenesis inhibition to chemotherapy. Post-operative mortality was very low (2%), however, both deaths occurred within the experimental arm.
CONCLUSION:	Overall, the study did not provide evidence for increasing efficacy of neoadjuvant chemotherapy by addition of angiogenesis inhibition by aflibercept. However, the results showed that waiver of radiotherapy seems to be a promising therapy option, which warrants further evaluation of radiotherapy-free treatment options in selected rectal cancer patient populations (middle / upper third with free CRM and a max infiltration of 10 mm regardless of the lymph node status).
Date of the report:	26.06..2023