

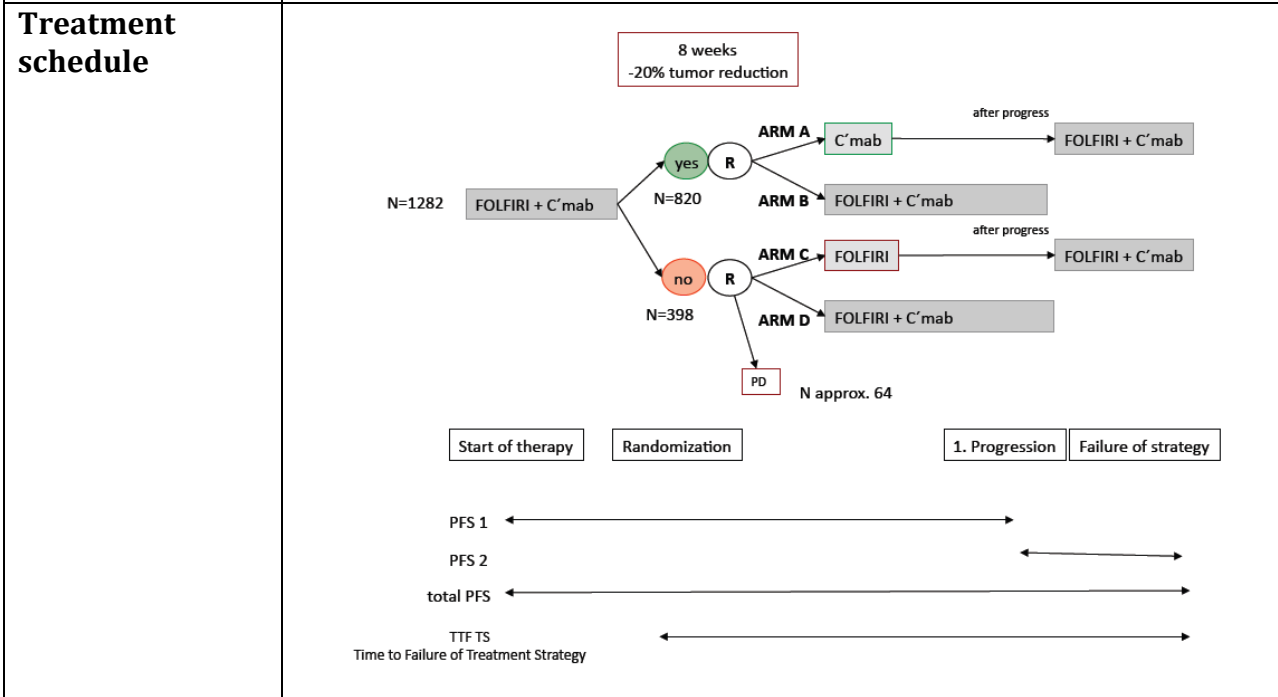
Shrinkage-Trial
Study Code: AIO-KRK-0111

Title of Study	De-escalation of 1st-line chemotherapy with palliative intention in patients with metastatic CRC (KRAS wild type) with or without early tumor shrinkage (ETS) under FOLFIRI-Cetuximab therapy – A phase III study
Principal Investigator	Prof. Dr. Dirk Arnold Director Hubertus Wald Tumorzentrum Universitäres Cancer Center Hamburg (UCCH) Universitätsklinikum Eppendorf Martinistr. 52 20246 Hamburg, Germany E-Mail: d.arnold@uke.de <i>for the Colorectal Cancer Working Group of the Arbeitsgemeinschaft Internistische Onkologie (AIO)</i>
Sponsor	AIO-Studien-gGmbH
Indication	Metastatic CRC
Proposed Countries	Germany (AIO, ADDZ), Denmark (confirmed) Spain (TTD), Ireland (ICORN), SWE, FIN, Australia (interested, under discussion) open for other countries Number of sites total: at least 120 (international) Number of sites @ AIO/ADDZ: tbd
Planned number of subjects and centers	Total Number of Subjects : 1282 Number of Subjects per (treatment) arm (if appl.): min. 2x410 for primary endpoint for patients with ETS and exploratively for patients without ETS: min. 2x199
Study design	Phase III, 1st line, two parallel arms, randomized, multicenter, multinational, open-label
Study objectives	<u>Primary objectives:</u> To evaluate and compare the time to failure of different treatment strategies: a) De-escalation of FOLFIRI in "responding" patients (Criteria according to Piessevaux et al., ESMO 2010) compared to continuation of FOLFIRI-Cetuximab combination. <u>Secondary Objectives:</u> To evaluate: <ul style="list-style-type: none"> • De-escalation of Cetuximab in patients without ETS compared to continuation of Cetuximab + FOLFIRI

	<ul style="list-style-type: none"> • PFS (total PFS, PFS 1, and PFS 2) • OS • objective remission rate • early tumor shrinkage rate (evaluations after 8 and 16 weeks) • Toxicity and Safety • QLQ
Study endpoints	<p><u>Primary Endpoint:</u> TTFS (Time to Failure of Treatment Strategy = Time from randomization until failure of reintroduction or maintained chemotherapy plus Cetuximab) for patients with ETS</p> <p><u>Secondary Endpoints:</u> <u>To evaluate:</u></p> <ul style="list-style-type: none"> • TTFS (Time to Failure of Treatment Strategy = Time from randomization until failure of reintroduction or maintained Cetuximab) for patients without ETS • PFS (total PFS, PFS 1, and PFS 2) • OS • objective remission rate • early tumor shrinkage rate (evaluations after 8 and 16 weeks)* • Toxicity and Safety • QoL/ PRO: QLQ C30, “fear of progression” (novel AIO), others tbd (in collaboration with AIO QoL Group) <p>*ETS after 16 weeks is exploratively evaluated for patients without ETS after 8 weeks only and correlated with outcome for evaluation as a possible additional predictive outcome measurement.</p>
Main inclusion criteria	<ul style="list-style-type: none"> • proven KRAS-wildtype tumor • unresectable metastatic colorectal carcinoma • no prior palliative chemotherapy • according to SPC
Main exclusion criteria	<ul style="list-style-type: none"> • potentially resectable liver limited disease • prior EGFR-targeted therapy • according to SPC • patients have to be free of tumor-related symptoms at the time of randomization (8 weeks after start of therapy)
Investigational Drug	<p>Name/Substance: Cetuximab Formulation: 5 mg/ml Dose: 400mg/m² “loading dose”, followed by 250 mg/m² weekly (induction phase; within first 8 weeks); during Cetuximab mono maintenance: 500 mg/m² fortnightly. Route: i.v. Duration: until progress</p>

Add-on Symptomatic patients (Investigators choice)

Name/Substance: **FOLFIRI**
 Formulation:
 Dose: FOLFIRI
 Irinotecan 180 mg/m² day1
 5-FU 400 mg/m² Bolus + 2400 mg/m² cont. i.v. for 46 h
 FA 400 mg/m² day 1
 Route: i.v.
 Frequency & treatment mode:
 Duration: 8 weeks and reintroduction after progress or until progression



Rationale for trial Sample size

Piessevaux et al. reported an analysis from the CRYSTAL study that patients with an “early response”, represented by tumor size shrinkage (sum of all lesions according to RECIST) of at least 20% after 8 weeks of FOLFIRI + Cetuximab had a median OS of 28.3 months and a median PFS of 11.8 months in comparison to 19.6 and 7.3 months for patients without “early shrinkage”. Interestingly, this large difference was not seen in the chemotherapy alone arm with a median OS of 21.2 vs. 20.2 and a median PFS of 9.7 vs. 7.7. The patients with an early shrinkage are possibly very sensitive to EGFR-inhibition. This raises the question, whether a de-escalation of the chemotherapy is a feasible option.

Therefore, the group of patients with an early shrinkage after 8 weeks (>= 20% remission) of FOLFIRI + Cetuximab – which represents ca. 65% of patients - will be randomised into Cetuximab monotherapy (biweekly) with reintroduction of chemotherapy after progression (Arm A) and into continuation of the chemotherapy combined with Cetuximab. (Arm B).

In a non-inferiority design the study will test the hypothesis that a de-escalation to Cetuximab monotherapy with reintroduction of chemotherapy by progression will not result in a significant decrease

	<p>in progression free survival (Time to Failure of Treatment Strategy = Time from randomization until failure of reintroduction or maintained chemotherapy plus Cetuximab) as compared to continued chemotherapy plus Cetuximab.</p> <p>By contrast, patients without early tumor shrinkage according to the mentioned criteria (ca. 35% of all patients @ week 8) may not benefit from Cetuximab at that extent. Therefore, this group of patients will be questioned whether continuation of Cetuximab is really necessary, and a randomisation between the continuation of FOLFIRI plus Cetuximab or FOLFIRI alone will be done (arms C, D). In this group, no formal testing will be done (exploratory analysis only)</p>
<p>Rationale for sample size and tests to be used</p>	<p>Sample size calculation/Assumptions: For the primary endpoint, Piessevaux et al. reported a median PFS of 11.8 weeks for continued FOLFIRI plus Cetuximab for patients with early shrinkage @ 8 weeks. Without the 8 weeks combination therapy the time from randomisation to progression will be some 10.0 month. A time of 8.0 months from randomisation to failure of treatment strategy for the de-escalated arm will be acceptable. This results in a non-inferiority margin for hazard ratio of 1.25. With 80% power and one-sided significance level (alpha) of 0.025, 675 progression events are required. With a fair number of drop-outs, a minimum of 820 patients are needed for randomization.</p> <p>There will be 2 interim analyses to check for futility or superiority. The first after 135 events (20%) and the second after 337 events (50%). At the interim analyses a DSMB will decide about pursuing the study based on the likelihood to show non-inferiority in the final analysis and recruitment rate.</p> <p>It is estimated that about 65% of the patients treated with FOLFIRI-Cetuximab will have an early shrinkage after 8 weeks of treatment. Considering the remaining 35%, a total of about 1282 patients are needed for screening after 8 weeks of treatment.</p>
<p>Interim/partial analyses required</p>	<ol style="list-style-type: none"> 1. Interim analysis after 135 events (about 300 randomized patients in Arm A+B, 450 screened) <ul style="list-style-type: none"> - ≈26.5 months after study start - study stop if HR > 1.40 (ie. P>0.7424) due to futility or - HR < 0.42 (ie. P<0.00000001) due to non-inferiority 2. Interim analysis after 337 events (about 620 randomized patients in Arm A+B, 970 screened) <ul style="list-style-type: none"> - ≈40 months after study start - study stop if HR ≥ 1.18 (ie. P>0.3055) due to futility or - HR < 0.72 (ie. P<0.00000015) due to non-inferiority <p>Final analysis after 675 events (820 randomized patients in Arm A+B,</p>

	<p>1282 screened)</p> <ul style="list-style-type: none"> - \approx 63 months after study start - HR \leq 1.0749 (ie. $p < 0.025$) would confirm non-inferiority - Equivalent to upper CI < 1.25 <p>It is estimated that the recruitment for Arms A and B will be 8/months in the first year, 12/months in the second year and 24/months in the 3rd and 4th year.</p>
How will the primary endpoint be analysed	CT-scan
How will the secondary endpoint be analysed	CT-scan Survival analysis Descriptive analyses
Study plan	<p>First Patient In (FPI): 07/2012 Last Patient In (LPI): 07/2015 Last Patient Off Treatment: 07/2016 Last Patient Last Visit (LPLV): 10/2017 Database Lock: 06/2018 (Integrated) Study Report Date: 12/2018</p>