Art der Erkrankung/ Entität, Therapielinie

PROTECTOR, Pre-Operative Treatment in rEseCTable cOlon cancer

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0620 - PROTECTOR		
Status:	in Vorbereitung		
Rekrutierungszeit:	von:	bis:	
Anzahl Zentren:	geplant: 80	aktuell initiiert:	aktiv rekrutierend:
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 525	aktuell eingeschlossen:	
Letzte Aktualisierung	09.12.2020		

STUDY TYPE	Intervention
PRINCIPAL INVESTIGATOR	**Medical Oncology:** Prof. Dr. med. Dominik Paul Modest, Med. Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin **Pathology:** Prof. Dr.med. Andrea Tannapfel, Institut für Pathology, Ruhr-Universität Bochum
TRIAL OFFICE	Prof. Dr. med. Dominik Paul Modest, Med. Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin
SPONSOR	Charité Universitätsmedizin Berlin
CONDITION	Colon cancer staged T3-4 and/or nodal positive without distant metastases.
DESIGN	Randomized, open-lable, Phase 3
INDICATION	Colon cancer
OBJECTIVE(S)	Preoperative therapy improves the outcome of patients with resectable colon cancer vs direct surgery followed by adjuvant therapy
INTERVENTION(S)	**Experimental intervention:** 12 weeks of neoadjuvant chemotherapy prior to surgery for colorectal cancer, followed by surgery **Control intervention:** direct surgery followed by standard of care adjuvant therapy
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	- ctDNA as a predictor for treatment response (or ctDNA level as predictors for response and survival) - QCL-IR-Imaging and artificial intelligence derived tissue based multivariate classifier for treatment response using neural networks - Influence of molecular subgroups on efficacy (consensus molecular subgroups, MAP-kinase alterations) - Immunprofiling and its influence on outcome parameters - Tumor regression according to Becker
BACKROUND/RATIONALE	The concept of perioperative therapy in advanced gastrointestinal cancers has raised momentum in various entities and represents standard of care in gastric/gastroesophageal junction cancers. The level of evidence in colorectal cancer is clearly driven by the management of rectal cancers with the development of total-neoadjuvant-therapy and also by the first colon cancer studies promoting pre-operative chemotherapy. Therefore, it can be concluded that the principle of neoadjuvant therapy in resectable abdominal cancers is established. Data from rectal cancer trials and also colon cancer suggest that the algorithm to establish early systemic therapy is safe and also likely associated with improved long-term

	outcome. We hypothesize that given the demonstrated effect size in FOXTROT with the adjustment of few design aspects (duration of therapy and exclusion of dMMR/MSI tumors as well as evaluation of accuracy of CT-based study entry), the strategy of neoadjuvant therapy in advanced colon cancer will improve disease-free survival.
KEY EXCLUSION CRITERIA	1. Not medically fit for surgery or chemotherapy 2. Acute bowel obstruction without intervention prior to study participation 3. Evidence of distant metastatic disease (indeterminate lung nodules with low clinical suspicion of metastases permitted)
KEY INCLUSION CRITERIA	1. Biopsy-confirmed adenocarcinoma of the colon 2. Proficient mismatch-repair system (pMMR) tested by immunohistochemistry or PCR 3. Radiologically (CT) staged disease as: T3-4 (as invasion of surrounding tissue structures or organs) **and/or** nodal positive (N+ defined as regional lymph node(s) without fat hilus and short axis diameter of ≥1cm), M0. 4. Intent for curative resection 5. Patients with bowel obstruction are only eligible if first stented or defunctioned 6. Tissue is available for pMMR/dMMR testing (centrally and/or locally) 7. Informed consent 8. Adequate bone marrow, liver, kidney, organ and metabolic function, 9. ECOG performance status 0 – 2 10. Age ≥ 18 at the time of registration
OUTCOME(S)	**Primary endpoint:** disease-free survival (DFS) **Secondary endpoint(s):** tumor regression score (TRS) by central review according to Dworak's score, overall survival (OS), safety of surgery, safety of chemotherapy, quality of life, treatments (including efficacy), outcome in molecular subgroups **Assessment of safety:** **For surgery:** length of hospitalisation, frequency of complication (anastomotic insufficiency, infections, redo surgery), 30/60 day morbidity and mortality **For chemotherapy:** NCI CTC AE assessment of toxicity,
STATISTICAL ANALYSIS	**Primary analysis:** The null hypothesis to be tested in confirmatory analysis states that the hazard ratio for DFS comparing intervention versus control equals 1. This hypothesis will be tested by means of Cox-regression adjusting for the above mentioned strata for randomization. The two-sided significance level is set to 0.05. The Cox-regression adjusted for additional factors provides a power advantage compared to the logrank test used for sample size calculation and this procedure thus provides a conservative approach. The primary analysis will be conducted based on the full analysis set which is defined as the intention to treat population. In a survival analysis setting, missing values are treated as non-informative censoring values so there is no need for imputation.
SAMPLE SIZE	Based on the best available evidence described above 2-year DFS is 70.0% in the straight to surgery group and we hypothesise that DFS will be 78% in the neo-adjuvant treatment followed by surgery group. To demonstrate an increase of 8 percentage points in 2-year DFS (hazard ratio = 0.696) requires observing 270 DFS events, with the recruitment of 525 (350:175 per arm) patients with an allocation ratio of 2:1 (experimental vs. standard). These calculations assume DFS follows an exponential distribution, a 2-sided 5% level of significance, 80% power, and allow for 2% dropout prior to meeting the DFS endpoint, with 5-year recruitment and 3-year follow-up periods. The event rate in the straight to surgery group will be monitored annually by the independent data monitoring and ethics committee to ensure these assumptions are appropriate.
TRIAL DURATION	102 Monate
PARTICIPATING CENTERS	Up to 80

FURTHER CENTERS DESIRED?	yes
NUMBER of PATIENTS	1000 screened, 525 recruited
CURRENT NUMBER of PATIENTS	0
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