AIO-LQ-0119/ass: Open-label, randomized, multicenter, phase IV trial comparing parenteral nutrition using Eurotubes® vs. traditional 2/3-chamber bags in subjects with metastatic or localized solid tumors requiring parenteral nutrition
- The PEKANNUSS Trial

AIO-assoziierte Studie

Studiennummer/-Code:	AIO-LQ-0119/ass - PEKANNUSS		
Status:	rekrutierend		
Rekrutierungszeit:	von: Nov. 2019	bis: Nov. 2022	
Zentren:	geplant: 50	aktuell initiiert: 20	rekrutierend: 14
Weitere Zentren:	sind sehr erwünscht		
Anzahl Patienten:	geplant: 350	aktuell eingeschlossen: 126	
Letzte Aktualisierung	16.03.2022		

STUDY TYPE	Open-label, randomized, multicenter, investigator-initiated phase IV trial
PRINCIPAL INVESTIGATOR	Prof. Dr. med. Salah-Eddin Al-Batran
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SPONSOR	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main, Germany
CONDITION	Patients with metastatic or localized solid tumors who have an indication for parenteral nutrition
DESIGN	This is an open-label, randomized, multicenter, investigator-initiated, phase IV trial. Patients with metastatic or localized solid tumors who fulfil the eligibility criteria and who have an indication for parenteral nutrition will be enrolled. Patients will be stratified according to ECOG (0-1 vs. 2 vs. 3), the modified Glasgow Prognostic Score (mGPS) (0-1 vs. 2) and whether the patient receives concurrent systemic anti-tumor treatment (e.g. chemotherapy, targeted therapy, immunotherapy) or not. In a first step, patients will be randomized in a 2:1 ratio to Arm A or Arm B: **Arm A: Standard Parenteral Nutrition using Eurotubes®.** or **Arm B: Standard Parenteral Nutrition using 2/3-chamber bags.** Patients randomized to Arm B will receive PN according to the routine used by the participating site. Patients in Arm A will be stratified again by the same criteria as listed above and randomized in a 1:1 ratio to Arm A-1 or Arm A-2: **Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®** Patients randomized to Arm A and in a second randomization to treatment Arm A-1 receive standard PN reduced in glucose in Eurotubes®. or **Arm A-2: Standard Parenteral Nutrition using Eurotubes®.**

	Patients randomized to Arm A and in a second randomization to treatment Arm A-2 will receive standard PN in Eurotubes®. Patients will be recruited during regular consultation visits. At screening and at all regular visits during the HPN treatment period (one visit per four-week interval after randomization for a maximum of 12 months) the ECOG performance status and body weight will be determined. Additionally, physical examinations and laboratory assessments including CRP, albumin and total protein levels will be performed. The HPN therapy plan and any modifications and adjustments to this plan during the course of HPN treatment will be recorded. Anti-cancer treatment at the time of screening and during the course of the HPN treatment period (e.g. type of treatment) will be documented. Monitoring of Adverse Events and medical device deficiencies will be performed at every visit. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. During the study the patient will maintain a study diary to document details of the administration of the HPN. A QoL questionnaire will be completed during regular study visits until EOT. After completion of study treatment, patients will enter the follow-up period. During this period, they will be followed approximately every 3 months for survival, which can be done by phone.
INDICATION	Patients with metastatic or localized solid tumors requiring parenteral nutrition
OBJECTIVE(S)	<u>Primary Objectives</u> *Co-Primary objective Catheter Related Infections (CRI)* • To compare the incidence of catheter related infections. *Co-Primary objective patient autonomy* • To compare the frequency of self-administered parenteral nutrition at home (HPN). <u>Secondary Objectives</u> • To compare the efficacy of parenteral nutrition (PN) in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS) • To compare the Quality of life (QoL) by use of the modified HPN-PROQ questionnaire • To determine the frequency and duration of visits by the nursing service • To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs) <u>Secondary Objectives (Arm A-1 vs. A-2)</u> • To compare the incidence of catheter related infections (CRI). • To compare the efficacy of PN in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS) • To compare the Quality of life (QoL) by use of the MODIFIED HPN-PROQ questionnaire

	• To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs)
INTERVENTION(S)	• **Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®** Patients randomized to Arm A and in a second randomization to treatment Arm A-1 receive standard PN reduced in glucose in Eurotubes®. • **Arm A-2: Standard Parenteral Nutrition using Eurotubes®.** Patients randomized to Arm A and in a second randomization to treatment Arm A-2 will receive standard PN in Eurotubes®. • **Arm B: Standard Parenteral Nutrition using 2/3-chamber bags.** Patients randomized to Arm B will receive PN according to the routine used by the participating site.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	N/A (no translational research)
BACKROUND/RATIONALE	Cancer is often characterized by extensive invasion, early metastases, and, in many cases, a rapidly occurring marked cachexia leading to a very poor prognosis especially in the metastatic situation. Cachexia is a strong and independent predictor of mortality, poor therapeutic response, diminished functional capacity, and reduced QoL. It is defined as the debilitating state of involuntary weight loss, often connected with anorexia, tissue wasting, malnutrition, and inability for natural nutrition intake. The combination of these symptoms is also named „cancer anorexia-cachexia syndrome" (CC). Approximately 50% of all cancer subjects suffer from CC and its severe impact on QoL and response to chemotherapy [Bossola et al., 2007]. Especially in the advanced stages, it cannot be fully cured by increased food intake or oral supplements and requires supportive or total parenteral nutrition. If needed, patients can live on PN for an unlimited time, the mean administration period depends much on the underlying disease, the ability to eat and the patient's general condition. However, data has shown that PN is accompanied by an increased risk of blood stream infections (BSI) [Dissanaike et al., 2007] and is an independent risk factor for both catheter-related bloodstream infections (CRBSI) and central line-associated bloodstream infections (CLABSI) [Beghetto et al., 2005]. BSI represent 15% of all nosocomial infections and are associated with increased mortality and other serious medical conditions such as severe sepsis or septic shock [Pontes-Arruda et., 2012]. In addition to the safety aspect, BSIs lead to longer hospital stays and hence, additional costs [Turpin et al., 2011]. Although most PN related BSI are caused by the intravenous catheter, numerous manipulations on the infusion unit may multiply the hazard of extrinsic contaminations [Didier et al., 1998]. To reduce this well-known risk, the relevant phases of PN (production, adding of supplements, administration) are subject to highest standards of hygiene in order to minimize the contamination risk. Industrial PN is manufactured following the guidelines of Good Manufacturing Practice (GMP) and under clean room conditions which reduces the contamination hazard significantly. Data indicate advantages of industrially manufactured PN compared to pharmacy-compounded PN formulations in terms of safety, however the limited data do not allow a definite conclusion [Turpin et al., 2012; Canada et al., 2009]. Furthermore, the change from oral food intake to PN is associated with many changes in the subject's everyday life that lead to restriction of autonomy and flexibility. CC patients are often unable to perform the PN procedure correctly

	on their own, especially when supplements need to be added. The nursing services need to visit the subject daily to perform the PN administration. The infusion takes around 12 to 14 hours to finish and is typically administered in the evening to be infused overnight. The subjects' daily life is highly determined by the appointments of the nursing service, overnight stays away are nearly impossible and the dependency on outside assistance can diminish the patients' self-esteem and QoL. The extent to which these limitations to the subject's self-determination can diminish the QoL is currently poorly studied and needs further investigation. Subsequently, it is of high interest to assess if the QoL shows to be higher in subjects performing the PN administration autonomously without nursing service assistance. Blood glucose levels and ketogenic diets are a contentious issue and subject of controversial discussion among oncologists. In the 1920s, Nobel laureate Otto Warburg observed that unlike healthy body cells, cancer cells strongly upregulate the glucose intake to produce energy preferably via glycolysis, instead of the much more efficient way of oxidative phosphorylation [Liberti and Locasane, 2016]. This phenomenon is known as the Warburg-Effect. Data hint that carbohydrate restriction and ketogenic diets possibly obstruct cancer growths [Klement and Kaemmerer, 2016], however, too little data is available to come to a definite conclusion. Thus, it will be another goal of the trial to collect data from patients with solid tumors receiving glucose-reduced PN and to examine if potential benefits regarding survival and other efficacy endpoints such as body weight can be observed.
KEY EXCLUSION CRITERIA	Patients who meet any of the following criteria will be excluded from study entry: 1. > 4 weeks of consecutive (≥ 3 days per week) parenteral nutrition in the last 3 months prior to study enrolment 2. Participation in another interventional clinical trial that could influence the endpoints of this trial or planned participation in such a study at the same time as this study is active (participation in other trials is possible in the follow up time for OS). The study is active, if the patients receive study treatment (PN), did not discontinue the trial for other reasons, and is still within the 12 months active study period 3. Current catheter related infection at baseline in patients with a suspected/proven previous conservatively managed catheter-related infection, a negative pair of blood cultures drawn from the central catheter is required. 4. Pregnancy or breastfeeding 5. Known hypertriglyceridemia ≥ CTCAE grade 3 6. Unable or unwilling to provide written informed consent and to comply with the study protocol 7. Uncontrolled diabetes mellitus 8. Congestive heart failure NYHA ≥ 3 9. Renal insufficiency GFR < 30 ml/min 10. Uncontrolled infection 11. Liver insufficiency
KEY INCLUSION CRITERIA	Patients* must meet the following criteria to be eligible for the study: 1. Age ≥ 18 years 2. Histologically confirmed metastatic or localized solid tumor. Perioperative setting of HPN is allowed if HPN is planned for a duration of ≥ 2 months 3. ECOG performance status of 0, 1, 2 or 3 4. Indication for PN (the subject needs a PN independent of the trial) 5. PN planned for 3 or more days per week

	6. Negative pregnancy test in women of childbearing potential 7. Willingness to perform double-barrier contraception during study for women of childbearing potential 8. Willingness to maintain a study diary 9. Life expectancy > 3 months 10. Written informed consent *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently.
OUTCOME(S)	**Primary endpoints** <u>Co-Primary endpoint catheter related infections (CRI)</u> Defined as the presence of bacteraemia originating from the intravenous (port) catheter – Bacteraemia must be confirmed through a blood culture according to study site-specific routine, preferably through paired quantitative blood cultures or a culture of the catheter if the catheter is removed – OR any infections originating from the intravenous (port) catheter, requiring intravenous antibiotics OR infections in the intravenous (port) catheter, requiring intravenous antibiotics or antibiotics delivered to the catheter itself or catheter removal. This also includes Catheter-related bloodstream infections (CRBSI), NOS, and Central line-associated bloodstream infections (CLABSI). For the diagnostic procedures to be done to confirm CRI, investigators are recommended to follow the DGHO guidelines. <u>Co-Primary endpoint patients' autonomy</u> The rate of self-administered parenteral nutrition at home (autonomy rate), defined as administration without nursing service assistance, as documented within the patient's study diary and calculated as the number of patients with autonomy divided by the total number of patients in the respective arm. Autonomy – as relevant for the primary endpoint – is achieved if the patient self-administers 50% or more of her/his total administrations (Note: Help of family members or other personal caregivers accounts for self-administration). **Secondary endpoints** <u>Efficacy endpoints</u> • Relative weight change determined at baseline and during study visits approx. every four weeks after enrolment; • Relative change of albumin and CRP levels measured at baseline and during regular study visits; • Overall survival (OS) defined as the time from randomization to death from any cause. <u>Quality of Life endpoints</u> • Quality of Life (QoL) through the MODIFIED HPN-PROQ questionnaire; • Frequency of PN-related visits by nursing service (as documented in the patients' diary). Safety endpoints • Catheter related complications such as line occlusions of catheter-related central venous thrombosis; • Severe, NCI-CTC common toxicity criteria version 5.0 grade 3-5, infections including fever of unknown origin and other Adverse Events according to NCI-CTC common toxicity criteria version 5.0; • PN-Related Adverse Events (AEs) and hospitalizations during therapy

STATISTICAL ANALYSIS	The primary analysis will compare patients randomized to Arm A (Standard Parenteral Nutrition using Eurotubes®) with those randomized to Arm B (Standard Parenteral Nutrition using 2/3-chamber bags) regarding the CRI rate and the objective patient autonomy and will be based on the ITT population. To test the hypotheses: H_{01}: "The CRI rate does not differ between the treatment Arms A and B (P11 = P21)." vs. H_{11}: "The CRI rate differs between the treatment Arms A and B (P11 ≠ P21)." and H_{02}: "The objective patient autonomy does not differ between the treatment Arms A and B (P12 = P22)." vs. H_{12}: "The objective patient autonomy differs between the treatment Arms A and B (P12 ≠ P22)." fisher's exact test is used with a type I error of 0.04 and 0.01, respectively.
SAMPLE SIZE	For both co-primary endpoints statistical significance is assessed using a fisher's exact test at a two-sided alpha level of 0.04 for the catheter related infections (CRI) rate and 0.01 for the objective patient autonomy, respectively. The power calculation was carried out using the Power Procedure in SAS version 9.4 (method: Walters normal approximation for unbalanced groups): Considering the 2:1 randomization, 226 patients must be included in Arm A (Standard Parenteral Nutrition using Eurotubes®) and 113 patients in Arm B (Standard Parenteral Nutrition using 2/3-chamber bags) to detect an improvement of the CRI rate from 25% (Arm B) to 10% (Arm A) with 90% power, resulting in a sample size of 339 patients. Concurrently, only 333 patients (222 in Arm A and 111 in Arm B) are needed to ensure 90% power to detect an improvement of the objective patient autonomy from 5% with traditional 2/3-chamber bags to 20% with Eurotubes®. Therefore, the patients' autonomy endpoint can be neglected for the sample size calculation. Assuming a dropout rate of about 3% it is planned to include 350 patients.
TRIAL DURATION	Patients will be observed for a maximum of 12 months of their PN starting from the date of randomization (except for OS which may be updated after the 12 months prior to data base closure). Physicians are free to continue PN after end of the observational period if they believe that PN is in the best interest of the patients, but this is done outside the study and is captured in the eCRF as post-discontinuation therapy. Recruitment is expected to occur over 3 years. The expected total study duration is 4.5 years.