Study Title:

An Open Label randomized multicenter Phase IIIb Trial comparing Parenteral Substitution versus Best Supportive Nutritional Care in Subjects with pancreatic adenocarcinoma receiving 5-FU plus Oxaliplatin as 2nd or Higher Line Chemotherapy regarding clinical benefit.

Short Title/ Acronym: PANUSCO

Final Study Report

Version Number/ Date:	Final 1.2, Update 09.03.2020
Investigational product:	Parenteral Substitution (SMOFKabiven®, Frekavit fat-soluble®, Frekavit water-soluble novum®, Tracitrans plus®, Omegaven®), 5-FU, Oxaliplatin
Eudra-CT Number:	2008-004696-22

Sponsor:
Universitätsklinikum Heidelberg
represented by its Commercial Director
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69120 Heidelberg, Germany

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Study Initiation and Completion Dates:
First Patient randomized: 03.08.2010
Early Termination of Study: 21.08.2014

Synopsis

Name of Sponsor/Company: Universitätsklinikum Heidelberg, represented by its Commercial Director
Name of Finished Product: IP 1: Drug Code: 5-Fluorouracil® (5-FU) Formulation: Solution for formulation of an infusion Manufacturer: Medac IP 2: Drug Code: Leucovorin® (FA) Formulation: Solution to be administered as a bolus injection Manufacturer: Wyeth Pharma IP 3: Drug Code: Eloxatin® (oxaliplatin) Formulation: Solution for formulation of an infusion Manufacturer: Sanovi-Aventis Deutschland GmbH IP 4: Drug Code: SMOFKabiven® Formulation: Emulsion for formulation of an infusion Manufacturer: Fresenius Kabi Deutschland GmbH IP 5: Drug Code: Tracitrans plus® Formulation: Concentrate for solution for an infusion Manufacturer: Fresenius Kabi Deutschland GmbH IP 6: Drug Code: Frekavit fat soluble® Formulation: Emulsion for formulation of an infusion with fat-soluble vitamins Manufacturer: Fresenius Kabi Deutschland GmbH IP 7: Drug Code: Frekavit water soluble novum® Formulation: Powder for solution for infusion Manufacturer: Fresenius Kabi Deutschland GmbH IP 8: Drug Code: Omegaven® Formulation: Solution for formulation of an infusion Manufacturer: Fresenius-Kabi Deutschland GmbH
Name of Active Ingredient: IP1: 5-Fluorouracil IP2: (S)-5-Formyl-5,6,7,8-tetrahydrofolic acid IP3: Oxaliplatin IP4: SMOFKabiven: Alanine, Arginine, Glycine; Histidine, Isoleucine; Leucine; L-Lysinacetate, Methionine, Phenylalanine, Proline, Serine, Taurine, Threonine,

Tyrosine, Valine, Sodiumacetate-3-aqua, Calciumchloride-2-aqua, Sodiumglycerolphosphate, Potassiumchloride, Magnesiumsulfate-7-aqua, Zincsulfate-7-aqua, Glucose-1-aqua, Soja Oil, Triglyceride, olive oil, Omega-3-acid

IP5: Sodiummolybdat 2 H2O, Sodiumselenit 5 H2O, Iron(III)-chlorid 6 H2O, Manganese (II)-chlorid 4 H2O, Copper (II)-chlorid 2 H2O, Chrome (III)-chlorid 6 H2O, Sodiumfluoride, Potassiumiodid, Zincchlorid

IP6: Retinopalmitat, Ergocalciferol, Phytomenadion; all-rac-alpha-Tocopherylacetat

IP7: Thiaminnitrat; Cyanocobalamin, Folic acid, Nicotinamid, Pyridoxinhydrochlorid, Riboflavin-5-phosphat-sodium 2 H2O, Biotin, Sodiumascorbat, Sosiumpantothenat

IP8: Omegaven: Icosapent, Doconexent; alpha-tocopherol, Glycerol, (3-sn-phosphatidyl) cholin

Title of Study:
An Open Label randomized multicenter Phase IIIb Trial comparing Parenteral Substitution versus Best Supportive Nutritional Care in Subjects with pancreatic adenocarcinoma receiving 5-FU plus Oxaliplatin as 2nd or Higher Line Chemotherapy regarding clinical benefit

Acronym: PANUSCO*, Protocol Version* Final 1.10, 26.10.2011

Protocol Version 1.5 from 31.08.2009 (First Authorization)

Protocol Version 1.8 from 13.01.2010, Amendment 03

Protocol Version 1.9 from 23.04.2010, Amendment 04

Protocol Version 1.10 from 26.10.2011, Amendment 11

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Publication (reference):

- Ockenga J, Valentini L. Review article: anorexia and cachexia in gastrointestinal cancer. Aliment Pharmacol Ther 2005;22:583-94.
- Bossola M, Pacelli F, Tortorelli A, Doglietto GB. Cancer cachexia: it's time for more clinical trials. Ann Surg Oncol 2007;14:276-85.
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- Sanjaya K, Siriwardena A. Systematic Review of Peri-Operative Nutritional Supplementation in Patients Undergoing Pancreaticduodenectomy. Journal of the Pancreas 2006;7:5- 13.
- Märten A, Wente MN, Ose J, Büchler MW, Rötzer I, Decker-Baumann C, Karapanagiotou-Schenkel I, Harig S, Schmidt J, Jäger D. An open label randomized multicentre phase IIIb trial comparing parenteral substitution versus best supportive care in subjects with pancreatic adenocarcinoma receiving 5-FU plus oxaliplatin as 2nd or higher line chemotherapy regarding clinical benefit, BMC Cancer.2009 Nov 27;9:412

Studied period (years): *incl. interruptions, early terminations and discontinuations*	*Phase of development:*
date of first enrolment: 03.08.2010 *date of last enrolment:* 11.09.2013 *date of last completed* 21.08.2014 *early termination of study* 21.08.2014 because of poor recruitment rate	Not applicable Phase III trial

Objectives: **Primary objective**:

Primary objective is the comparison of the treatment groups with respect to event-free survival (EFS). EFS is defined as the time from randomization till time to development of an event defined as either an impairment (change from baseline of at least ten points in EORTC QLQ-C30, functional domain total score) or withdrawal due to fulfilling the stopping criteria for chemotherapy or parenteral nutrition (PN) and Best Supportive Nutritional Care (BSNC) in Arm A or BSNC alone in Arm B or death from any cause (whichever occurs first).

BSNC is defined as nutritional consultation and recommendation by experienced ecotrophologists.

Secondary objectives:

Comparison of the treatment groups with respect to tumor-cachexia, Objective Response Rate (ORR), Time to Progression (TTP), Progression Free Survival (PFS), Overall Survival (OS), Toxicity, time from randomization till time point when stopping criteria are met, definition and evaluation of a scoring system identifying subject groups who will benefit from second line chemotherapy and/or parenteral nutrition.

Methodology:

PANUSCO was a controlled, open-label, prospective, randomized; phase IIIb, multicentre trial with two parallel arms testing parenteral nutrition and BSNC versus BSNC alone in subjects with pancreatic adenocarcinoma receiving 2nd or higher line chemotherapy with 5-

FU and oxaliplatin, BSNC being defined as nutritional consultation and recommendation by experienced ecotrophologists.

This study was conducted in eight medical centers in Germany. Clinical Monitoring was done by ECRON ACUNOVA GmbH, while pharmacovigilance was handled by spm² - safety projects & more GmbH. Biometrical planning was done by the NCT Heidelberg, while data management and statistical analysis were provided by the Institute for Medical Biometry and Informatics (IMBI), Heidelberg.

In PANUSCO, 31 patients suffering from advanced pancreatic adenocarcinoma with previous progression under chemotherapy were enrolled. For allocation of the participants, an internet-based randomization system (randomizer.at) was used with a 1:1 allocation ratio, stratified for the factor Eastern Cooperative Oncology Group Performance Status (ECOG PS; stratum 1: PS < 2, stratum 2: PS ≥ 2). Randomisation was done using fixed block sizes. According to randomization status, patients either received chemotherapy, BSNC and PN, or chemotherapy and BSNC only. Blinding of participants was not conducted.

Table 1 shows a flow chart of visits, interventions, and data collected for the outcomes.

	Screening/ Baseline	**Enrolment**	**Cycle 1**						**Cycle 2**						**Cycle 3[e]**		**EoT**
Day	Max. -14	Between Screening and 1st intervention	1	8	15	22	29	36	43	50	57	64	71	78	85	…	
Visit	Screening	0	1	2	3	4	5	6	7	8	9	10	11	12	13	…	
Histology	X																
Medical History	X																
Informed Consent		X															
Pregnancy test[a]	X																
Randomisation		X															
ECOG-Status	X		X			X			X			X			X	…	X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	…	X
Physical exam.	X		X			X			X			X			X	…	X
Chemistry	X		X			X			X			X			X	…	X
Complete blood count /differential blood count	X		X	X	X	X	X	X	X	X	X	X	X	X	X	….	X
Carbohydrate-Antigen 19-9			X						X						X	…	X
CT Abdomen	X[d]								X						X	…	X[d]
Nutritional Status[b]			X			X			X			X			X	…	X
24 h recall	X		X	X	X	X	X	X	X	X	X	X	X	X	X	…	X
Quality of Life			X			X			X			X			X	…	X

Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	…	X
5-FU/FA		X	X	X	X			X	X	X	X			X	…	
Oxaliplatin			X		X				X		X				…	
Parenteral nutrition		Continuously on six days a week (only arm A) [f]														

[a] For women with childbearing potential

[b] BIA, BMI, biceps size, hand-grip strength, NRS questionnaire, PINI

[d] CT until progression of disease

[e] to be continued until meeting stopping criteria

[f] End of Study-Treatment Visit

Number of patients (planned and analyzed):

Planned 120 patients

Randomized 31 patients

Analyzed 31 patients

Diagnosis and main criteria for inclusion: Subjects with advanced pancreatic adenocarcinoma with previous progression under chemotherapy

Main inclusion criteria:

- Written informed consent
- Histological confirmed advanced pancreatic adenocarcinoma
- At least one previous chemotherapy (gemcitabine-based)
- ≥ 18 years old
- Body weight ≥ 50 and ≤ 95 kg
- BMI ≥ 19
- Negative pregnancy test (females of childbearing potential)
- Willingness to perform double-barrier contraception during study
- Life expectancy > 3 months

Main exclusion criteria:

- Major surgery < 4 weeks prior to enrolment
- Weight loss > 2% within the last seven days or caloric intake ≤ 500 kcal expected within the next five days
- Prognostic and Inflammatory Nutritional Index (PINI)-Index > 10
- Pregnancy or breastfeeding
- > 4 weeks of Parenteral Nutrition within the last 6 months
- Parenteral Nutrition < 4 weeks of enrolment
- Vulnerable populations (e.g. subjects incapable of giving consent personally)
- Subject selection conflicts with warnings, precautions and contraindications stated for any investigational product

Test product, dose and mode of administration, batch number:

5-FU is a cytotoxic agent approved for the treatment of pancreatic adenocarcinoma. 5-FU is given IV. It is combined with FA to improve the efficacy of 5-FU. Manufacturer of 5-FU is Medac. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to the Summary of Product Characteristics (SPC).
Batch-No.: Use of marketable goods, Batch-No. are not available

Leukovorin® (a folinic acid) is a medication used to decrease the toxic effects of 5-fluorouracil. For further information see SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Oxaliplatin is a cytotoxic agent approved to be combined with 5-FU and FA. It is supplied as an aqueous solution for IV injection. Manufacturer of oxaliplatin is Sanofi-Aventis Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to the SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

SMOFKabiven® is an emulsion used for PN. It provides amino acids, carbohydrates and fat to be given IV. Furthermore, SMOFKabiven® contains a special fat-combination consisting of soybean oil, medium-chain-triglycerides, olive oil and fish oil (SMOF®). It is approved for supplementation of amino acids, fat and carbohydrates as PN in subjects where oral or enteral nutrition is impaired, impossible or contraindicated. Manufacturer of SMOFKabiven® is Fresenius Kabi Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to the SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Frekavit fat-soluble® is an emulsion used for the substitution of fat-soluble vitamins within the application of PN. It is indicated as a supplement in intravenous nutrition to meet the daily requirements of the fat-soluble vitamins A, D2, E and K1. Manufacturer of Frekavit fat-soluble® is Fresenius Kabi Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to the SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Frekavit water-soluble novum® is an infusion concentrate of water-soluble vitamins. It is indicated in adult patients as a supplement in intravenous nutrition to meet the daily requirements of water-soluble vitamins. Manufacturer of Frekavit water-soluble novum® is Fresenius Kabi Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Tracitrans plus® is a concentrate for solution for an infusion. It is indicated in patients as a supplement in intravenous nutrition to meet basal to moderately increased requirements of trace elements and an increased zinc demand within long-term PN. Manufacturer of Tracitrans plus® is Fresenius Kabi Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application to the medication it is referred to the SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Omegaven® is an emulsion to be given IV. It is approved for supplementation of omega-3 fatty acids in PN for subjects where oral or enteral nutrition is impaired, impossible or contraindicated. Manufacturer of Omegaven® is Fresenius Kabi Deutschland GmbH. For further information regarding contraindications, interactions and warning notices for application of the medication it is referred to the SPC.
Batch-No.: Use of marketable goods, Batch-No. are not available

Chemotherapy:

5-Fluorouracil (5-FU) 2000mg/m2 IV (24-hour)/folinic acid (FA) 200mg/m2 IV (30 min) were administered weekly over four weeks with additional oxaliplatin 85 mg/m2 IV (2-hour) on days 8 and 22. Therapy was interrupted between days 23 to 42. The next cycle was started on day 43. Therapy was given until a study withdrawal criterion (disease progression, unacceptable toxicity or subject's consent withdrawal) was met.

Experimental group (arm A):

The subjects in the experimental group received BSNC and parenteral supplementation (over night with SMOFKabiven®, Omegaven®, Frekavit fat-soluble®, Frekavit water-soluble novum® and Tracitrans plus®). PN was given continuously on six days a week. PN was discontinued during chemotherapy. Every kind of enteral nutrition and oral supplementation was allowed.

Duration of treatment: The treatment duration was expected to be approximately four months including three months of chemotherapy for each subject.

Reference therapy, dose and mode of administration, batch number:

Chemotherapy (all subjects):

5-Fluorouracil (5-FU) 2000mg/m2 IV (24-hour)/folinic acid (FA) 200mg/m2 IV (30 min) was administered weekly over four weeks with additional oxaliplatin 85 mg/m2 IV (2-hour) on days 8 and 22. Therapy was interrupted between days 23 to 42. The next cycle was started on day 43. Therapy was given until a study withdrawal criterion (disease progression, unacceptable toxicity or subject's consent withdrawal) was met.

Control group (arm B):

Subjects in the control group received solely BSNC. Every kind of enteral nutrition and oral supplementation was allowed.

Criteria for evaluation:
Due to the preliminary and incomplete state of the database at the time of the report, only the primary endpoint event-free survival and the safety variables Adverse and Serious Adverse Events could be analyzed for this report.

Efficacy: Primary objective is the comparison of the treatment groups with respect to event-free survival (EFS). EFS is defined as the time from randomization till time to development of an event defined as either

- an impairment (change from baseline of at least ten points in EORTC QLQ-C30, functional domain total score)
- or withdrawal due to fulfilling the stopping criteria for chemotherapy or NI in both study arms, i.e.
    - intervention (NI for both study arms and chemotherapy) was stopped in case of unacceptable toxicity appears. Unacceptable toxicity is defined as unexpected serious side effects or irreversible Grade 4 toxicity.
    - Chemotherapy was stopped in case of progression. Progression is defined according to revised RECIST criteria Version 1.1
    - NI was stopped for individual subjects in both study arms when two of the following three stopping-criteria are met:
        - weight loss > 2% within the last 7 days or caloric intake ≤ 500 kcal expected within the next 5 days,
        - BIA defined by phase angle and Body Cell Mass (BCM) with a deterioration higher than 10% (in both parameters) detoriation compared to baseline assessment,
        - Prognostic and Inflammatory Nutritional Index (PINI)-index > 10 (only in subjects with no sign of acute inflammation),
- or death from any cause (whichever occurs first).

Safety: Frequency of Adverse Events and Serious Adverse Events

Statistical methods:

Primary efficacy analysis:

A stratified logrank test was used to compare the two treatment arms regarding the primary variable stratified by the ECOG PS (stratum 1: PS < 2, stratum 2: PS ≥ 2).

The EFS-rates are derived from the Kaplan Meier estimate and the confidence intervals were calculated using Greenwood's formula (PROC LIFETEST in SAS). The above method relies on the assumption that events are recorded at the time they occur and there is no lag in the time at which they are reported.

Handling of missing data

The primary variable, EFS, is defined as the time from randomization till time to development of an event defined as either an impairment (change from baseline of at least ten points in EORTC QLQ-C30, functional domain total score: five functional scales (physical, role, cognitive, emotional, and social) or withdrawal due to fulfilling the stopping criteria (refer to section 4.6) or death from any cause (whichever occurs first). Missing data in the EORTC QLQ-C30 questionnaire post baseline was to be imputed using multiple imputation.

For patients who are not known to have died, the last known survival date was taken as the latest date in the database from the following recorded dates:

- sample date for laboratory assessment or any other data which required a sample
- visit date for clinical/imaging response or any other response data
- last date of dosing on dosing log
- date of onset or resolution from adverse event log.

At any time after this last known survival date the subject had a status of 'Censored' in terms of overall survival. Any patients who withdrew from the study for a reason other than death (i.e. lost to follow-up) were censored on the day of withdrawal from the study.

One formal interim analysis of efficacy and safety was originally scheduled to be performed after the first 47 events (ca. 50% of the events) had occurred. The nominal one-sided significance levels for the interim analysis were set to be 0.0026 and 0.0240 respectively.

Due to unplanned termination of the study, no interim analysis was conducted. The final analysis was performed as done in a fixed sample size design at a descriptive two-sided significance level of 0.05.

Safety analysis:
Safety data was summarized for all subjects in the safety population.

Sample size calculation:

The sample size was calculated to detect differences in the 4-month EFS-rates and is based on a comparison of two groups using the unstratified log-rank test. The 4-month EFS-rates were assumed to be 60% and 40% (Hazard ratio=0.557) in the experimental and control group. Applying one interim analysis according to group sequential design with two stages using the O'Brien and Fleming type, a 1:1 randomization, and assuming an accrual time of 36 and a follow-up time of 4 months a total of 102 patients and of 93 events were required for a two-sided log-rank test with an overall two-sided significance level of 0.05 and power of 0.80. With the expectation that approximately 15% of patients may be lost to follow up, it was estimated that 120 patients would need to be enrolled. Formula of Schoenfeld (Biometrica, 1981, 316-319) was used for the calculation of the number of events. ADDPLAN, Version 4.0 was used for the sample size estimation.

Study populations:

Three analysis populations were defined.

Intent-to-Treat (ITT) population:

The ITT population includes all subjects who are randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects receive study drug or receive a different drug from that to which they were randomized. This is the primary population for evaluating all efficacy endpoints.

Safety population:

The safety population consists of all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population is the primary population for evaluating treatment administration/compliance and safety.

Per protocol (PP) population:

The PP population consists of all subjects of the ITT population who completed at least one chemotherapy cycle, have at least 2 post-baseline assessments regarding the primary endpoint without pre-specified, selected major protocol deviations thought to impact on efficacy analysis.

SUMMARY - CONCLUSIONS

Since, due to unfinished data queries, the database was not locked yet at the time of this report, all following results are preliminary results based on the state of the trial database on 05.08.2015

EFFICACY RESULTS:

Event free survival:

One patient had a missing baseline value in EORTC QLQ-C30 score. His primary outcome was accordingly set to missing and hence the sample size for the primary efficacy analysis only amounted to n=30.

In the ITT population, median EFS in group A was 50 days (95%-CI=[31;134]), while in group B it was 76 days (95%-CI=[26, 173]). EFS rates at 4 months were 27.27% in group A and 35.29% in group B.

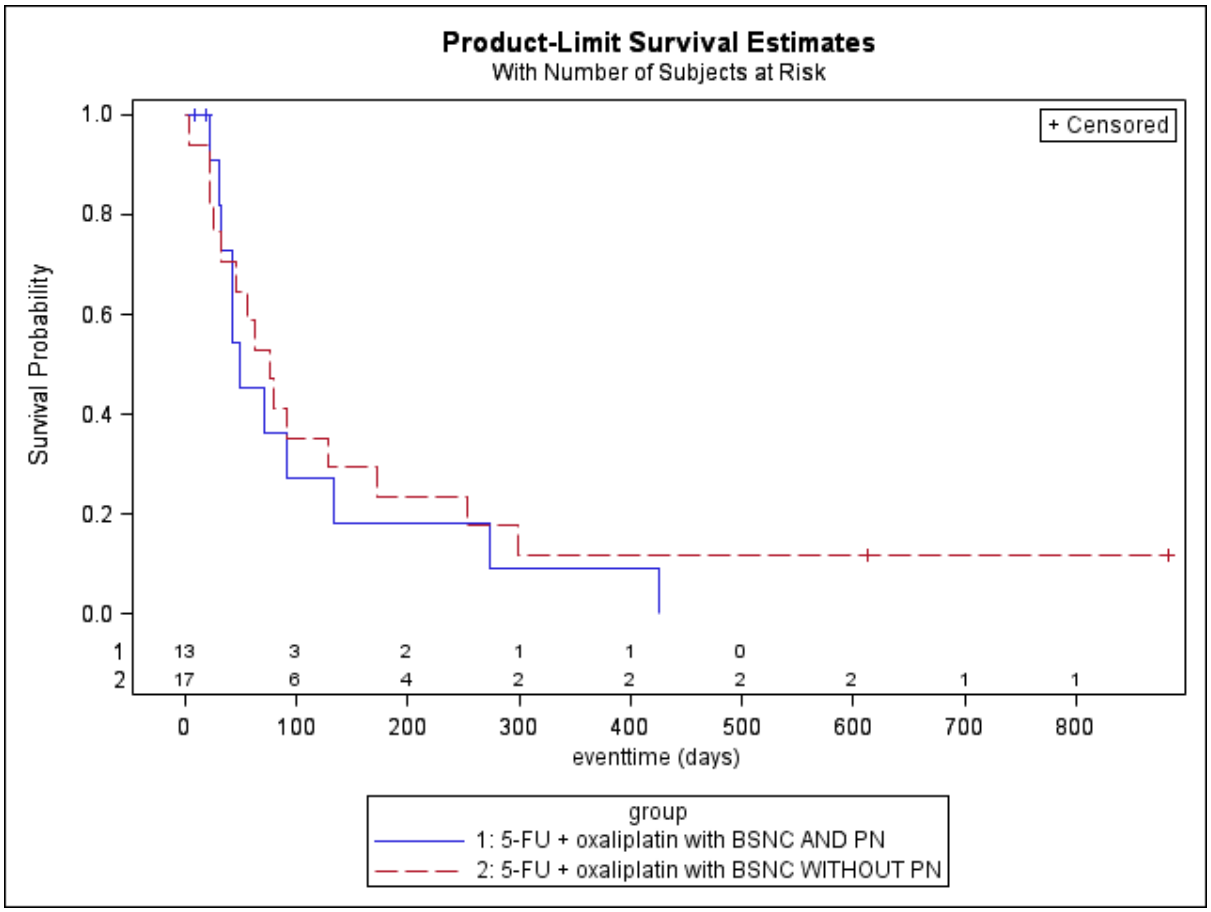

Fig.1: Kaplan-Meier estimate for survival probability and number of subjects at risk

For the primary efficacy analysis, a stratified log-rank test with strata ECOG PS (stratum 1: PS < 2 (n=30), stratum 2: PS ≥ 2 (n=1)) comparing the two treatment arms, multiple imputation was used to impute missing EORTC QLQ-C30 scores post baseline. Three patients had one missing EORTC QLQ-C30 score each before they left the trial. Hence 8 imputed datasets containing all possible scenarios (event/no event for the respective patient at the respective time point with missing value in EORTC QLQ-C30) were constructed, and the results of the multiply imputed datasets were pooled for the test of efficacy according to the method of *Rubin, D.B. (1987) Multiple Imputation for Nonresponse in Surveys. J. Wiley & Sons, New York*. The p-value of this stratified log-rank test was p=0.59, hence there was no significant difference between the treatment groups in terms of event-free survival.

As a sensitivity analysis, a stratified log-rank test on the original dataset without imputed values was calculated. The resulting p-value was p=0.43, hence confirming the result of the primary analysis that there was no significant difference between treatment arms.

SAFETY RESULTS:

The safety population comprised 12 patients in group A and 19 patients in group B since one patient which was randomized to treatment A withdrew his informed consent after already receiving a first cycle of chemotherapy, but prior to the start of PN.

Number of AEs in group A were 155, number of patients with AEs was 12 (100%), while in group B, number of adverse events was 207, which were experienced by 18 patients (94.7%).

Number of SAEs in group A was 8, number of patients with SAEs was 4 (33.33%), while in group B, there were 14 SAEs, which were experienced by 5 patients (26.3%).Further characteristics about AEs and SAEs are depicted in Table 2.

Table 2. Characteristics of adverse and serious adverse events

	5-FU + oxaliplatin with BSNC AND PN n=12			5-FU + oxaliplatin with BSNC WITHOUT PN n=19			Total n=31		
	# AE	# patients with AE		# AE	# patients with AE		# AE	# patients with AE	
Intensity									
- Grade 1	56	10	(83.3%)	104	14	(73.7%)	160	24	(77.4%)
- Grade 2	59	11	(91.7%)	80	16	(84.2%)	139	27	(87.1%)
- Grade 3	38	9	(75.0%)	23	11	(57.9%)	61	20	(64.5%)
- Grade 4	2	1	(8.3%)	0	0	(0.0%)	2	1	(3.2%)
Countermeasures									
- none	42	9	(75.0%)	110	14	(73.7%)	152	23	(74.2%)
- drug treatment	81	10	(83.3%)	80	18	(94.7%)	161	28	(90.3%)
- others	32	7	(58.3%)	17	7	(36.8%)	49	14	(45.2%)
Chemotherapy: Action									
- Dose not changed	98	12	(100.0%)	172	17	(89.5%)	270	29	(93.5%)
- Dose rduced	7	3	(25.0%)	11	7	(36.8%)	18	10	(32.3%)
- Drug/intervention temporarily discontinued	30	3	(25.0%)	10	5	(26.3%)	40	8	(25.8%)
- Drug/intervention withdrawn	5	3	(25.0%)	2	1	(5.3%)	7	4	(12.9%)
- Unknown	1	1	(8.3%)	5	2	(10.5%)	6	3	(9.7%)
- Not applicable	14	3	(25.0%)	7	4	(21.1%)	21	7	(22.6%)
Chemotherapy: Causality									
- possible	55	9	(75.0%)	74	11	(57.9%)	129	20	(64.5%)
- unrelated	77	9	(75.0%)	48	8	(42.1%)	125	17	(54.8%)
- not assessable	23	8	(66.7%)	84	13	(68.4%)	107	21	(67.7%)
Nutritional intervention: Action									
- Dose not changed	101	11	(91.7%)	116	15	(78.9%)	217	26	(83.9%)
- Dose reduced	1	1	(8.3%)	1	1	(5.3%)	2	2	(6.5%)
- Dose increased	5	3	(25.0%)	1	1	(5.3%)	6	4	(12.9%)
- Drug/intervention temporarily discontinued	12	3	(25.0%)	0	0	(0.0%)	12	3	(9.7%)
- Unknown	1	1	(8.3%)	15	2	(10.5%)	16	3	(9.7%)
- Not applicable	35	5	(41.7%)	74	8	(42.1%)	109	13	(41.9%)
Nutritional intervention: Causality									
- possible	24	4	(33.3%)	12	2	(10.5%)	36	6	(19.4%)
- unrelated	104	10	(83.3%)	83	10	(52.6%)	187	20	(64.5%)
- not assessable	27	7	(58.3%)	110	14	(73.7%)	137	21	(67.7%)
Outcome									
- recovered/resolved	52	9	(75.0%)	92	15	(78.9%)	144	24	(77.4%)
- recovering/resolving	34	5	(41.7%)	21	4	(21.1%)	55	9	(29.0%)
- not recovered/not resolved	44	7	(58.3%)	40	7	(36.8%)	84	14	(45.2%)
- fatal	0	0	(0.0%)	3	1	(5.3%)	3	1	(3.2%)
- unknown	25	7	(58.3%)	51	13	(68.4%)	76	20	(64.5%)

CONCLUSION:

Since the originally planned sample size was not achieved, the planned power is not reached

and all results can be interpreted only descriptively.

In terms of the primary objective event-free survival (EFS), there was a slight non-significant disadvantage for group A as compared to group B (p=0,43). However, the obtained results have no confirmatory value and are only of descriptive and exploratory character. Therefore no treatment recommendations can be made out of these trial results.

A critical point to consider is the fact, that EFS includes the factors quality of life (LQ), course of disease, tolerance of therapy and nutritional factors (see Efficacy). These factors can improve or worsen independently from one another and are not obligatory independent of the nutritional intervention. Therefore a separate analysis of the single factors could potentially give more significance. Unfortunately due to the incompleteness of the database obtained, evaluation of these factors cannot be assessed.

A comparative evaluation of AEs cannot be made due to low group sizes. In group A more AEs graded 3 and 4 were observed. In both groups nutritionally induced AEs were registered. Group B received only BSNC so that an AE can be correlated more effectively. However Group A received PN and BSNC, so it is not possible to determine whether the AE was due to PN or BSNC. Therefore it is not possible to evaluate or make any presumptions from this collected data.

In group A 24 AEs and group B 12 AEs were observed with a nutritional correlation. The higher number of AEs in group A can be explained by the fact, that some of group A participants received PN, an invasive nutritional therapy. In contrast group B participants received a non-invasive nutritional therapy. Taken into consideration that PE (an invasive therapy) was given up to 6 times per week over the entire trial duration, the occurrence of 24 AE cases is actually very low. In this case it seems that chemotherapy supported with PE is a feasible and safe form of nutritional therapy.

Substantial amendments / interruptions or early termination:

Protocol Versions:

Final 1.5, 31.08.2009	First Authorization
Final 1.8, 13.01.2010	Translational aspect of study was deleted from protocol, outline was changed
Final 1.9, 23.04.2010	Definition of Primary Objective was revised to reveal that end of chemotherapy/end of BSNC/PN is an event and it is not mandatory that both end at the same time. The term End of Study visit was revised to harmonize the terms in the protocol and the CRF.
Final 1.10, 26.10.2011	Addition of one paragraph Exclusion criteria, trial duration

Early Study termination: The PANUSCO trial was terminated early after 31 patients were randomized. On August 21st 2014, the competent authority, involved ethics committees, and local authorities were notified about the trial termination.

Date of the report: 09.03.2020