Statistical Analysis Plan for NORDIC9-study Quality of Life analysis

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Title:

The effects of palliative chemotherapy on quality of life in vulnerable older patients with metastatic colorectal cancer:

Statistical analysis plan (SAP) for secondary analyses from the randomized NORDIC-9 trial

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Background and study rationale:

Only little is known about quality of life, functional status, and symptom burden in vulnerable older patients with metastatic colorectal cancer receiving palliative chemotherapy. Oncologists are usually interested in traditional tumor-centered endpoints **(1-3)** used in randomized controlled trials (RCTs) of cancer drugs. Overall survival (OS) is considered as the gold standard primary endpoint **(1)** of efficacy in RCTs. When several treatment lines are available, measuring OS may be challenging. Therefore, surrogate outcomes for OS like progression-free survival and response rates have been widely used. Whether these surrogate outcomes are valid for OS or may be considered as relevant markers for expanded length of survival or quality of life, is questionable. Undoubtedly, if one treatment results in prolonged survival and less toxicities over another treatment, thus, showing clear benefits, choosing the better option is easy for the physicians and patients **(4, 5)**. On the contrary, when two treatment options gain the same survival benefit, but differ with regards to toxicity and adverse events, evaluation of patient-reported quality of life is of huge importance **(6)**. This may add valuable information to optimize shared decision-making processes between clinicians, patients and caregivers in choosing the treatment that suits their clinical condition best. Furthermore, an important aspect when it comes to later line palliative treatment, is that quality of life tends to worsen across treatment lines **(7)** due to disease progression, increasing tumor burden, and cumulative toxicities.

Despite incidence and mortality rates top in adults' aged ≥70 years, older patients with cancer are highly underrepresented in RCTs **(8-11).** Thus, the older population is generally treated based on extrapolated data from highly selected younger and healthier cohorts. However, as older individuals often have comorbidities and impaired organ function, the drugs tested in the RCTs may be less effective and more toxic in the elderly population, thus negatively affecting quality of life. This is problematic, as older patients with cancer tend to prioritize improvement or preservation of quality of life **(12-14)**, rather than prolonged survival.

RCTs addressing quality of life and patient-centered endpoints have long been desired not only by researchers and physicians **(15-19)**, and the leading cancer societies **(20, 21)**, but by the regulatory authorities **(11, 22)** like the European Medicines Agency and the U.S. Food and Drug Administration as well. However, QoL or other patient-centered endpoints are either not included in RCTs of cancer drugs at all **(2, 3**), or if they nevertheless are, the results are often insufficiently reported due to methodological and practical issues **(23)**. In a systematic review of phase III colorectal cancer trials conducted between 2012 and 2018, including 67 studies, Lombardi and colleagues found that 61.2% of these trials did not include quality of life as endpoint **(2)**. In 38.5% of those trials including quality of life among endpoints in their primary publication, quality of life data was not yet reported. In RCTs investigating treatment options in the metastatic setting, where attention to quality of life seem highly important due to limited life expectancy, quality of life data was not available in 66.7% of trials with OS as primary endpoint and in 69% of trials with other primary endpoints. This stresses the importance of appropriate conducting and reporting of RCTs.

The present study examines the effects of palliative chemotherapy on quality of life, functional status, and symptom burden in vulnerable older patients with metastatic colorectal cancer. The current study includes secondary and exploratory analyses of data collected in the NORDIC-9 trial **(24, 25)**. The Nordic-9 trial was a prospective, randomized open-label phase II multicenter study including older vulnerable patients with metastatic colorectal cancer aged ≥70 years, *not* candidate for standard combination chemotherapy treatment. The detailed protocol, study design, primary endpoint, and several secondary endpoints of this prospective, randomized open-label phase II study has already been published **(24, 25)**. The primary analysis showed that reduced-dose combination chemotherapy (S1+oxaliplatin) resulted in significant longer median progression free survival, fewer toxicity, and less hospitalization compared to full-dose monotherapy (S1). The study design, adverse events, progression free-, and overall survival data has been described in detail elsewhere **(25)**. When we designed NORDIC9-trial, we aimed for prolonged PFS with reduced-dose combination therapy, though expecting somewhat higher risk of adverse events given that two cytotoxic agents were administered simultaneously. Therefore, we also wanted to prospectively evaluate patient-reported quality of life as well as physician-reported functioning according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores. Given the primary finding of the NORDIC-9 trial with significant longer PFS for the S1+oxaliplatin arm it is essential to also show that the prolonged PFS do not come at the expense of poorer quality of life compared to full-dose S1 monotherapy arm.

In the present study, we hypothesize that treatment with reduced-dose S1+oxaliplatin does not result in inferior quality of life as measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) compared to treatment with full-dose S1 monotherapy. Further to this, we also hypothesize that treatment with S1+oxaliplatin do not result in inferior physical functioning as evaluated by ECOG PS compared to treatment with full-dose S1 monotherapy alone.

Objectives and outcomes:

Primary*:*

The primary objective of the current analyses is to test the hypothesis that treatment with reduced-dose combination chemotherapy (S1+oxaliplatin) is not inferior to the full-dose monotherapy (S1) in terms of affecting global quality of life. We will compare the impact of S1+oxaliplatin vs. S1 on changes in overall QoL as assessed by the EORTC QLQ-C30 global QoL domain from randomization to 9-week follow-up. Changes in the global quality of life domain will thus be the primary outcome measure.

The rationale for choosing the global quality of life domain as primary outcome measure is that this domain reflects the patients' self-perceived general health and quality of life. While RCTs investigating the effect of cancer drugs on patient-reported outcomes have shown that even grade 3 non-hematological clinician-reported toxicities do not affect global quality of life **(26, 27)** and that the value of using global quality of life as primary outcome in clinical trials has been questioned due its low sensitivity to changes **(28)** we strongly believe this to be an important outcome in the NORDIC-9 trial. The reason is that this trial included older patients with incurable cancer and limited life expectancy, thus expecting to prioritize general wellbeing and QoL over prolonged survival. Further to this, the effect of palliative

chemotherapy on global quality of life has not been extensively studied in older vulnerable populations.

Secondary:

Key secondary objectives:
This includes exploration of the effects of S1+Oxaliplatin relative to S1 on other clinically important patient-reported outcome (PRO) measurements in the following EORTC QLQ-C30 subscales: 1) physical functioning, 2) role functioning, and 3) social functioning between the two arms from baseline and at 9-week follow-up.

Hypothesis:
Here, we choose functioning items considered as having a key role in older patients regarding the maintenance of their general physical and mental wellbeing. We assume that reduced-dose combination treatment (S1+Oxaliplatin) does not result in inferior outcomes compared to full-dose monotherapy (S1) regarding the domains above.

Other secondary objectives:
We will investigate if there is a difference in the EORTC QLQ-C30 symptom domains and single items; 1) fatigue, 2) dyspnea, 3) nausea and vomiting, 4) diarrhea between the two trial arms from baseline to 9-week follow-up according to the toxicity profile of the applied cytostatic agents.

Hypothesis:
Given the toxicity profile of the applied cytotoxic agents and the adverse events reported in primary publication of the NORDIC9-trial, we assume that patients receiving full-dose monotherapy (S1) may experience higher symptom burden compared to reduced-dose combination treatment (S1+Oxaliplatin)

We are going to establish the risk of deterioration in physician-reported physical functioning by the ECOG PS score at 9-week follow-up.

Hypothesis:
Risk of deterioration is higher in patients receiving full-dose monotherapy.

Data collection and timing of outcome assessments
EORTC QLQ-C30 paper based questionnaire was completed at baseline, at 9-week, and at 18-week follow-up by the patients. The ECOG PS scores were registered by the treating physician at baseline, thereafter subsequently every three weeks until the end of the trial participation. However, only values at 9- and 18-week follow-up were derived from the patients´ medical record and used in the present study.

Study population

The current analyses will be based on the intention to treat (ITT) population of the randomized NORDIC9-trial, including all randomized patients receiving ≥1 dose of chemotherapy and completing at least one quality of life assessment.
In total, 160 patients were included, of those 150 received at least one dose of chemotherapy. The ten patients who did not receive treatment were thus excluded and has been described in detail elsewhere **(25)**.

Study outcomes

Patient-reported outcomes on quality of life:
The EORTC QLQ-C30 questionnaire **(29)** contains a global quality of life scale, five functioning scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact). The questionnaire asks about the last one-week time frame at completion and uses a four-point response format ("not at all," "a little," "quite a bit," and "very much"), except for the global QoL scale using a seven-point response format ranging from "very poor" to "excellent". The different scale and item scores are linearly transformed to a score between 0-100 according to the scoring manual. For global QoL and the functioning scales, a higher score indicates better outcomes, for symptom scales, a higher score reveals more prominent symptoms. Scoring will be conducted according to the QLQ-C30 scoring manual.

Clinician-reported outcomes:
The ECOG PS score is the most frequently used clinical score in oncology daily practice and research. This tool provides an overview of the patients' physical performance. The ECOG PS score has six possible values where 0 means that the patient is "fully active, able to carry on all pre-disease performance without restriction" and 5 means that the patient is "dead".

Compliance with completion of patient-reported outcomes

Compliance will be calculated using the proportion of randomized patients with completed questionnaires (EORTC QLQ-C30) and the proportion of patients expected to complete questionnaires (alive and still on study). This will be tabulated per trial arm at baseline and at then subsequently for all scheduled visits (e.g. at 9-week and 18-week follow-up).

Statistical consideration and analyses metrics

Formal sample size calculation for the PRO data was not performed. Hence, the current sample follows the sample size needed for the primary endpoint of the NORDIC9-trial. This has been described in detail elsewhere **(25)**.

For the patient-reported outcomes:
The primary statistical model for the patient-reported outcomes will consist of linear mixed effects model for repeated measures (MMRM) including all PRO assessments (e.g. baseline, 9-, and 18-week follow-up). This allows us to compare the average treatment effect of full-dose monotherapy (S1) vs. reduced-dose combination (S1+ Oxaliplatin) treatment.

These analyses will be performed as non-inferiority analyses reporting coefficients with 95% confidence intervals for mean differences and comparing with mean minimal important differences as reported by Musoro et al. **(31)**. As it is not certain, that the baseline PRO measurements were performed before the patient and healthcare professionals were informed about the result of the randomization, the treatment effect will therefore be included also at baseline. Methodological discussion of this consideration can be found elsewhere **(32)**.
As a sensitivity analysis a Bayesian linear mixed effects model (fitted by MCMC) with weakly informative symmetric priors (N(0,10000)) for regression coefficients and weakly informative (IGamma(0.01,0.01)) priors for variance components will be applied reporting posterior probabilities of superiority, non-inferiority, equivalence, and inferiority.

For the clinician-reported outcomes:
Deterioration of ECOG PS score from baseline to 9- and 18-week follow up will be defined as a ≥1-point decline from baseline and will be analyzed using logistic regression. In the main analysis, discontinuation of the study participation for any reason will be regarded as deterioration of performance. In sensitivity analyses "A" only discontinuation due to death will be considered as deterioration, while patients who left the study for other reasons will be excluded. In sensitivity analysis "B" only observed ECOG PS will be used to define deterioration and any patients who left the study will be excluded.

All data will be analyzed in STATA v16 (StataCorp LLC, Texas, USA.). P-value ≤0.05 will be considered significant and estimates will be reported with 95% confidence intervals.

Adjustment for multiplicity
As only global quality of life is considered a primary outcome, while the other outcome are considered secondary and supportive of the primary outcome, no adjustment for multiplicity will be performed.

Missing data, sensitivity analyses and robustness
Missing data in the PRO analyses will be handled by restricted maximum likelihood estimation in the of linear mixed effects model assuming missing by random. Missing data in the ECOG PS analysis will be handled by the two pre-specified sensitivity analyses (See above).
Sensitivity analyses are specified above for the different analyses.
Acceptable fulfillment of model assumptions will be investigated by normal quantile-quantile plots for residuals and random effects in the linear mixed models, in case of deviations nonparametric bootstrapping with 1000 repetitions will be performed.
Performance of the MCMC algorithm applied in the Bayesian models will be investigated by diagnostic plots (trace, autocorrelation and posterior kernel density). In case of signs of insufficient performance thinning as well as additional MCMC chains will be applied.

Goodness of fit of the logistic regression model will be investigated by Hosmer-Lemeshow's test.

Interpretation

In general, each PRO domain will be interpreted according to clinically relevant minimally important differences (MID) using guidelines for between-group differences and change over time **(31, 35)**.

Primary outcome:

For the global QoL domain, the result will be interpreted according to the anchor-based MID for between-group differences as reported by Musoro et al. **(31)**. Based on the principles related to non-inferiority designs, we pre-specify that a 95% confidence interval excluding negative differences between groups of greater than -8.13 points (the mean MID for deterioration) in global QoL would be interpreted as indicating the absence of a clinically meaningful inferiority difference.

	Anchor-based MID for within-group change		Anchor-based MID for between-group difference in change	
Scale	Improvement	Deterioration	Improvement	Deterioration
PF	7.31–8.52 (7.81)	−8.43 to −6.09 (−7.47)	6.05–10.04 (7. 69)	−7.23 to −4.16 (−5.96)
RF	10.43–18.06 (14.24)	−10.66	7.95–14.17 (11.06)	−9.96
SF	8.11–10.26 (9.23)	−6.18	6.73–7.79 (7.28)	−6.03
QL	7.14–10.34 (8.43)	−7.97 to −4.83 (−6.38)	5.53–6.36 (5.86)	−9.12 to −6.81 (−8.13)
FA	7.65–13.82 (10.79)	−7.73 to −7.05 (−7.38)	5.43–12.01 (8.77)	−6. 98 to −6.76 (−6.87)
NV	7.75	−7.95 to 5.30 (−6.62)	7.34	−7.33 to −5.17 (−6.25)
AP	12.28	−9.78	10.0	−7.11
DI	6.35	−7.96	8.25	−5.46
CO	12.75	No MID	14.56	No MID

Secondary patient-reported outcomes:

For functioning domains (physical functioning, role functioning, social functioning) and symptom domains/single items (fatigue, dyspnea, nausea and vomiting, diarrhea) the results will be interpreted according to the anchor-based mean MID for deterioration for between-group differences as shown in the figure above **(31)**. However, as the symptom domain of dyspnea was not included in the paper by Musoro et al **(31)**, the dyspnea domain will be interpreted according to the MID scores of the EORTC evidence-based guidelines for between-group differences **(34)**. A medium between-group difference, corresponding to at least 9 points, will be used as the threshold.

Clinician-reported outcome:

Risk of deterioration will be compared between the two treatment groups according to the analysis specified above.

Ethics

National ethical committees in all respective countries have approved the NORDIC9-study, which has been conducted according to the Declaration of Helsinki and Good Clinical Practice

guidelines. The manuscript will be prepared according following the Consolidated Standards of Reporting Trials guideline extended with patient-reported outcome recommendations (CONSORT PRO guideline)**(33)**.

Planned tables and figures:

Table 1: Baseline characteristics of study participants

Characteristics Data presented as mean or n (%) as appropriate.	**NORDIC9-study treatment arms** **Patients available for QoL analysis (n=150)**	
	Full-dose monotherapy **Arm A** **n=**	Reduced-dose combination CT **Arm B** **n=**
Age (years) Mean (SD) 70-74 75-79 ≥ 80		
Sex Male Female		
ECOG Performance status 0 1 2		
Location of primary tumor Right sided Left sided		

Unknown		
Surgery for primary tumor Yes No		
Prior adjuvant chemotherapy Yes No		
Presentation at diagnosis Synchronous Metachronous		
Number of metastatic sites 1-2 3≤		
Sites of metastatic disease Liver Lung Peritoneum Others		
Surgery for metastases Yes No		
RAS mutation status Wild type Mutant Unknown		
BRAF mutation status Wild type Mutant Unknown		

Self-reported weight-loss >5% within the last 2 months Yes No		

Table 2. Measurements by treatment group and time point

	Baseline		9 weeks		18 weeks	
EORTC QLQ-C30 domains	Monotherapy	Reduced combination therapy	Monotherapy	Reduced combination therapy	Monotherapy	Reduced combination therapy
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Global QoL						
Physical functioning						
Social functioning						
Role functioning						
Fatigue						
Nausea and vomiting						
Diarrhea						
Pain						

Table 3: PRO measurements by treatment group and time point

EORTC QLQ-C30 domains		Change from baseline to 9 weeks				Change from baseline to 18	
		Monotherapy	Reduced combination therapy	Difference		Monotherapy	Reduced combinatio therapy
		Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	P-value	Coefficient (95% CI)	Coefficient (95% CI)
Global QoL	C30 Global QoL						
Physical functioning	C30 Role function						
Social functioning	…						
Role functioning							
Fatigue							
Nausea and vomiting							
Diarrhea							
Pain							

Table 4: Bayesian analysis of PRO measurements

EORTC QLQ-C30 domains	Change from baseline to 9-week follow-up				Change from baseline to 18-week follo		
	Superiority	Non-inferiority	Equivalence	Inferiority	Superiority	Non-inferiority	Equivalence
	Posterior probability						
Global QoL							

Physical functioning							
Social functioning							
Role functioning							
Fatigue							
Nausea and vomiting							
Diarrhea							
Pain							

Table 5: ECOG PS deterioration, counts and proportions

	Baseline		9-week follow-up		18-week follow-up	
	Monotherapy	Reduced combination therapy	Monotherapy	Reduced combination therapy	Monotherapy	Reduced combination therapy
	Main analysis					
PS=0						
PS=1						
PS=2						
	Sensitivity analysis A					
PS=0						
PS=1						
PS=2						
	Sensitivity analysis B					
PS=0						
PS=1						
PS=2						

Table 6: ECOG PS deterioration, associations

	9 -week		18-week	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Main analysis				
Sensitivity analysis A				
Sensitivity analysis B				

Figures:

Global QoL over time as line-diagram with 95% CI

Posterior distribution of difference in global QoL at 9 weeks (supplemental)

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