Statistical analysis plan addendum for Patient-Reported Outcomes in the LyRICX study: Liposomal iRInotecan, Carboplatin or oXaliplatin in the first line treatment of esophagogastric cancer: a randomized phase 2 study

Addendum to: *Statistical analysis plan for the LyRICX study: Liposomal iRInotecan, Carboplatin or oXaliplatin in the first line treatment of esophagogastric cancer: a randomized phase 2 study*, **version 1.0, dd 15-05-2025**

Addendum version: 1.0, dd 06-03-2026.

Full title of the study: Liposomal iRInotecan, Carboplatin or oXaliplatin in the first line treatment of esophagogastric cancer: a randomized phase 2 study
Short title of the study/acronym (optional): LyRICX
ABR number: 66783
Research protocol: EU CT number: 2023-509287-26-00 Protocol version: 6.0, 28-03-2025
Trial registration number: NCT03764553 https://clinicaltrials.gov/study/NCT03764553?term=Lyricx&rank=1

Content

Section 1. Administrative information.

1.1. Names and Signatures

Role of contributor	Name and full affiliation	Signature	Date of signature
Principal investigator	Prof. dr. Hanneke W.M. van Laarhoven, Department of Medical Oncology, Amsterdam UMC,	[redacted]	10-3-2026
Principal investigator	Dr. Nadia Haj Mohammad, Department of Medical Oncology, University Medical center Utrecht	[redacted]	8-3-2026
Researcher who will perform the statistical analysis	Drs. Denice Kamp, Julius center for health sciences and primary care, University medical center Utrecht	[redacted]	10-03-2026
Senior statistician consulted	Dr. Rob Kessels, Julius center for health sciences and primary care, University medical center Utrecht	[redacted]	6-3-2026

Section 2. Scope of this addendum

This addendum describes the statistical analyses for patient-reported outcomes (PRO's) in the LyRICX study. This addendum is to be read in conjunction with the main statistical analysis plan (SAP) and does not modify analyses unrelated to PRO's. All statistical principles and methods not explicitly described in this addendum follow the main Statistical Analysis Plan.

Section 3. Statistical analysis methods for patient reported outcomes

3.1 Questionnaires and scoring

Patient-reported outcomes (PRO) for patients included in LyRICX were collected through the Prospective Observational Cohort Study of Esophageal-Gastric Cancer Patients (POCOP).[1] The EORTC QLQ-CIPN20 was sent out at registration to POCOP, and every 3 weeks thereafter. The EORTC QLQ-C30 and EORTC QLQ-OG25 were sent out at registration and every 12 weeks thereafter. The EORTC QLQ-CIPN20 consists of 3 symptom subscales (sensory, motor, and autonomic) and a total score. The EORTC QLQ-C30 consists of 15 scales, including five functional scales, three symptom scales, a global health status/quality-of-life scale, and six single symptom items. The EORTC QLQ-OG25 consists of 6 multi-item symptom scales and 10 single symptom items specific to esophagogastric cancer. All scores will be transformed linearly to a 0-100 scale, with higher scores indicating better functioning or global health status for functional scales and global health, and higher scores indicating more severe symptoms for symptom scales and single items, as per EORTC scoring manuals.[2]
Missing items within a PRO scale will be handled according to EORTC scoring guidelines: if ≥50% of the items required to calculate a scale are available, the scale score will be calculated based on the mean of the completed items, if <50% of the items are available, the scale score will not be calculated.[2]

3.2 Analysis population and follow-up

PRO's will be analysed until the progression-free survival event (defined as progressive disease according to RECIST 1.1 or death, whichever occurs first) for each patient. Patients without a PFS event at data cut-off for primary analyses will be analysed until their censoring date.

Analyses will primarily be performed in the intention-to-treat population. As sensitivity analyses, the same models will be fitted in the per-protocol population.

3.3 Timepoint definitions

Baseline and follow-up timepoints are defined using prespecified visit windows.

- **Baseline**
  Baseline is defined as any assessment performed from 6 months before randomisation up to 3 weeks after randomisation and, if systemic treatment (LyRICX or other) is initiated, up to 7 days after start of treatment. A maximum of one baseline assessment per patient will be selected. If multiple baseline assessments are eligible, the assessment closest to treatment start will be selected for patients who started treatment, and the assessment closest to randomisation will be selected for patients who did not start treatment.
- **Follow-up timepoints**
  All follow-up assessments must be performed after randomisation and, if a baseline assessment is available, after baseline. A maximum of one questionnaire per

patient is allowed per timepoint. If multiple questionnaires are completed within the same timepoint window, the questionnaire completed closest to the nominal timepoint will be selected.

For the EORTC QLQ CIPN20 questionnaire, follow-up timepoints are defined as:

- 3 weeks: 8-31 days after randomisation
- 6 weeks: 32-52 days after randomisation
- 9 weeks: 53-73 days after randomisation
- Subsequent 3-week intervals thereafter, up to a maximum timepoint of 51 weeks (347-367 days after randomisation).

For the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires, follow-up timepoints are defined as:

- 3 months (=12 weeks): 8–100 days after randomisation
- 6 months (=24 weeks): 101–184 days after randomisation
- 9 months (=36 weeks): 185–268 days after randomisation
- 12 months (=48 weeks): 269–370 days after randomisation

3.4 Longitudinal analyses

PRO's will be analysed longitudinally to evaluate changes over time and compare treatment arms. For each PRO scale, two linear mixed-effects models will be fitted:

1. **Mixed model without baseline adjustment (using all available data):**

   This model will include all patients with at least one PRO assessment (baseline and/or follow-up):

   - Fixed effects will include:
     - Trial arm
     - Time (as factor, baseline and follow-up timepoints as defined above)
     - Trial arm x time interaction
     - Stratification factors used at randomisation: performance status, presence of liver metastasis, synchronous vs metachronous metastatic disease
   - A random intercept, and if necessary, a random slope, for each patient to account for repeated measures within individuals

2. **Mixed model with baseline adjustment:**

   This model will include patients with a baseline assessment and at least one post-baseline assessment.

   - Fixed effects will include:
     - Baseline score
     - Trial arm
     - Time (as factor, follow-up timepoints as defined above)
     - Trial arm x time interaction

    - Stratification factors used at randomisation: performance status, presence of liver metastasis, synchronous vs metachronous metastatic disease
- A random intercept, and if necessary, a random slope, for each patient to account for repeated measures within individuals

The results of these two models will be compared to assess the influence of baseline PRO adjustment on treatment effect estimates.

3.5 Presentation of results

Baseline PRO scores will be summarised descriptively by treatment arm using means and standard deviations.

Estimated marginal means with 95% confidence intervals derived from the mixed models will be presented in tables and graphically displayed for each PRO scale, timepoint, and treatment arm.
Differences in estimated marginal means with 95% confidence intervals will be reported for the following pairwise treatment comparisons at each timepoint:

- CapCar vs F-Nal-IrI
- F-Nal-IrI vs CapOx
- CapCar vs CapOx

These between-arm differences will be interpreted in relation to established minimally clinically important differences (MCIDs). For the EORTC QLQ-CIPN20 the following MCIDs will be applied:

1. Sensory subscale: 2.5-5.9[3]
2. Motor subscale: 2.6-5.0 [3]
3. Autonomic subscale: no established MCID available, will be interpreted descriptively
4. Total score: 6.2-8.4 [4]

For all EORTC QLQ C30 and OG25 subscales a MCID of 10 points will be applied.[5]

As PRO's are secondary endpoints and analyses are considered exploratory, therefore no adjustment for multiple testing will be made.

References

1. Coebergh van den Braak, R.R.J., et al., *Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative.* Acta Oncol, 2018. **57**(2): p. 195-202.
2. Fayers PM, A.N., Bjordal K, Groenvold M, Curran D, Bottomley A, *The EORTC QLQ-C30 Scoring Manual (3rd ed.)*. 2001, Brussels, Belgium: European Organisation for Research and Treatment of Cancer.
3. Yeo, F., et al., *Minimal clinically important difference of the EORTC QLQ-CIPN20 for worsening peripheral neuropathy in patients receiving neurotoxic chemotherapy.* Support Care Cancer, 2019. **27**(12): p. 4753-4762.

4. Li, T., et al., *Patient-Reported Outcome Measures in Chemotherapy-Induced Peripheral Neurotoxicity: Defining Minimal and Clinically Important Changes*. J Natl Compr Canc Netw, 2023. **21**(2): p. 125-132 e3.
5. Osoba, D., et al., *Interpreting the Significance of Changes in Health-Related Quality-of-Life Scores*. J Clin Oncol, 2023. **41**(35): p. 5345-5350.