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 of this SAP: 1.0; 15-05-2025

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
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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, AmsterdamUMC,	[signature redacted]	23-5-2025
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Senior statistician consulted	Dr. Rob Kessels, Julius center for health sciences and primary care, University medical center Utrecht	[signature redacted]	17-06-2025

1.2. Revision history

Updated statistical analysis plan version	Protocol version	Section number(s) changed	Description of and reason for changes	Date of approval
1.0 (current)	6.0	-	-	15-05-2025

1.3. How is the trial registered?

This study was initially registered in EudraCT (EudraCT number: 2018-002767-26) and has since transitioned to the EU Clinical Trial Register via CTIS (EU CT number: 2023-509287-26-00). Additionally, the study is also registered at ClinicalTrial.gov under the identifier NCT03764553.

1.4. What is the planned period of observation?

The actual date of the inclusion of the first patient was 10-09-2019. The expected date of the completion of follow-up for the last patient is 20-07-2025.

Section 2. Introduction.

2.1. What is the background and rationale for the study?

No globally accepted standard first-line treatment regimen for advanced gastric and esophageal cancer exists. Therefore, in this study we will compare three F-doublets, both in terms of efficacy and toxicity, and specifically neurotoxicity, to identify the most optimal first-line cytotoxic treatment regimen for future use. The first doublet is capecitabine in combination with oxaliplatin (CapOx), which is a frequently used doublet in many countries, and, in fact, in the Netherlands even the most frequently used doublet. Given the neurotoxicity of oxaliplatin, as a second F-doublet we will introduce capecitabine with carboplatin (CapCar) as an alternative platinum compound, which is expected to give substantially less neurotoxicity than oxaliplatin. Finally, as a third doublet, we will replace the platinum compound by liposomal irinotecan (Nal-IRI), which, supposedly, will lead to hardly any or even no neurotoxicity.

2.2. What are the objectives of the study?

The primary objective is to compare the progression free survival and neurotoxicity of first-line treatment with F-Nal-IRI, CapCar and CapOX.
The secondary objectives are:

- To determine the overall survival of F-Nal-IRI, CapCar and CapOx.
- To determine the response rate of F-Nal-IRI, CapCar and CapOx.
- To determine the adverse events of F-Nal-IRI, CapCar and CapOx according to NCI CTCAE version 5.0.
- To determine patient reported outcome measures of F-Nal-IRI, CapCar and CapOx treated patients.
- To determine the percentage of patients proceeding to subsequent lines of treatment after progression and describe the types of subsequent treatments.
- To determine the reasons for forgoing subsequent treatment after progression on first-line treatment.
- To compare the primary secondary objectives for patients treated with and without nivolumab.
- To compare the progression free survival after reintroduction of carboplatin, oxaliplatin or Nal-IRI (=PFS2: time from reintroduction after first moment of disease progression, until disease progression) with the progression free survival after start of second line treatment (= time from start until discontinuation of second line treatment).

This statistical analysis plan covers the primary and secondary objectives, but does not include the exploratory objectives, which are listed in section 2.3 of the protocol.

Section 3. Study Methods.

3.1. What is the study design?

This study is a multi-center, open label randomized phase II clinical trial, using a pick the winner design. Patients will be randomized to one of three arms:
1. *F-Nal-IRI*: Nanoliposomal irinotecan, leucovorine, fluorouracil
2. *CapCar:* Capecitabine and carboplatin, with or without Nivolumab
3. *CapOx:* Capecitabine and Oxaliplatin, with or without Nivolumab
Detailed information on the three treatment regimens can be found in the study protocol in section 6,7 and 8 respectively.

We start from the assumption that neuropathy is the toxicity that affects the start of subsequent treatment regimens most, while also significantly affecting quality of life of patients. Furthermore, we hold the principle that if a treatment regimen conveys long lasting neurotoxicity, this should be balanced out by a substantial benefit in (progression-free) survival. As the F-Nal-IRI doublet is expected to have the lowest neurotoxicity, this will be used as the comparator.

Estimand:
Population: patients with histologically confirmed metastatic or irresectable HER2 negative adenocarcinoma of the stomach or oesophagus, not pre-treated with systemic therapy for irresectable or metastatic disease, and with measurable disease as assessed by RECIST 1.1
Treatments: F-Nal-IRI, CapCar, or CapOx
Primary endpoints: progression free survival (PFS) 1 and neurotoxicity
Strategy to handle intercurrent events: treatment policy, The intercurrent event is considered irrelevant in defining the treatment effect (intention-to-treat analysis)

3.2. Will randomization be performed in this study?

A total of 320 patients are individually randomized in ALEA clinical software (Version 17.1). Randomization is stratified by ECOG (WHO) performance score, presence of liver metastases and having recurrent versus primary metastatic disease using block randomization. No blinding is performed in this study.
Until August 2022 all patients were randomized between the F-Nal-IrI, CapCar and CapOx arms in a 2:2:1 ratio respectively.
In the second quarter of 2022, addition of Nivolumab to treatment with a fluoropyrimidine and a platinum compound was approved in the Netherlands for patients with advanced gastroesophageal adenocarcinoma and a Programmed-death ligand 1 (PD-L1) combined positive score (CPS) of five or more. From August 2022 onwards, patients will be tested for PD-L1 and then will be conditionally randomized. Patients with a PD-L1 CPS <5 or a contraindication for nivolumab treatment, will be randomized to respectively F-Nal-IrI, CapCar and CapOx arms in a 2:2:1 ratio. Patients with a PD-L1 CPS ≥5 will be randomized to the CapCar and CapOx arms following a 2:1 ratio and will receive nivolumab in addition to chemotherapy treatment. With the introduction of this conditional randomization, the method for stratification was changed to the minimization technique (instead of the previous block randomization).

3.3. How was the sample size calculated?

The original sample size calculation was based on a survival analysis with exponential means using the F-distribution, which did not align with the proposed analysis strategy for the primary endpoint (logrank test). Furthermore, the moment when the final analysis should take place

(official study completion) was not specified in the protocol. Therefore, in protocol version 6.0 the sample size was re-evaluated using the logrank test with a minimum follow-up period of 12 months for each patient. In addition, the actual accrual period took longer than the initial assumed accrual period (64.5 months versus 36 months), which is also considered in the re-evaluated sample size determination. The new sample size calculation is now event-driven and we calculated the minimum number of events needed to obtain 80% power for all comparisons. Consequently, the final analysis will take place when the last randomized patient has been followed for 12 months or when the minimum number of required events has been reached earlier in which case the final analysis will take place when all randomized patients have at least minimum of 6 months follow-up for sufficient neurotoxicity observations.

The sample size to identify the best combination therapy is based on the following decision-making strategy. With less or even zero neurotoxicity grade 2-4, the Nal-IRI plus 5FU combination is expected to outperform the standard combination capecitabine plus oxaliplatin and may also outperform capecitabine plus carboplatin. To compensate for a higher neurotoxicity grade 2-4 level, the capecitabine combinations should demonstrate increased (median) PFS of 3 or 4 months, depending on difference in neurotoxicity (Cf Table 2) With the addition of nivolumab in the second quarter of 2022, the capecitabine combinations are expected to have an additional PFS benefit over the Nal-IRI of 0.85 months (50% of the 1.7 months seen in the CM649[5], because 50% of patients in the capecitabine arms are expected to be treated with nivolumab, see table 17)

Table 1. Expected inclusion of patients before and after the addition of nivolumab

	CapOx	CapCar	F-nal-IRI	
Included before addition of nivolumab	20	40	40	100
Included after addition of nivolumab	48	96	28	172
Of which PD-L1 CPS <5	*14*	*28*	*28*	70
Of which PD-L1 CPS ≥5	*34*	*68*	*0*	102
Total	68	136	68	272 (/0.85=320)

Table 2. Decision making strategy

Difference in % neurotoxicity grade 2-4	Compensating increase in median PFS	Compensating increase in median PFS with addition of nivolumab in 50% of patients in capecitabine arms compared to F-Nal-Irl
>10-30%	3 months	3.85 months
30-50%	4 months	4.85 months

If the difference in the percentage of patients experiencing neurotoxicity grade 2-4 stays within the 10-30% range, an increase of at least 3.85 months of median PFS identifies the most preferable capecitabine combination strategy in comparison with F-Nal-IRI. For determining the 'winner' amongst the capecitabine combinations, a difference in PFS of at least 3 months must be demonstrated, if the difference in the percentage of patients experiencing neurotoxicity grade 2-4 stays within the 10-30% range. At least 4 or 4.85 months PFS should be gained to compensate for a difference in neurotoxicity grade 2-4 within the >30 to 50% range when comparing the capecitabine combinations among themselves or with Nal-IRI plus 5FU combination, respectively.

If the difference in the percentage of patients experiencing neurotoxicity grade 2-4 is ≤10% when comparing F-Nal-Irl to one of the capecitabine combinations, the capecitabine combination is preferable. If the difference in percentage of patients experiencing neurotoxicity grade 2-4 among the capecitabine combinations is ≤10% and the PFS increase <3 months, but in favor of carboplatin,

then the choice should be based on other grade 3-4 toxicities observed; otherwise, the strategy with the lowest level of neurotoxicity grade 2-4 is the most preferable one.

In general, the standard median PFS is expected to be about 6.5 months. The calculated minimum power and required events for detecting the compensating PFS difference between the arms considering a difference in neurotoxicity of >10-30% is presented in Table 3, assuming a minimum total number of randomized patients of 272 (see Table 1). Power is calculated using a one-sided logrank test with an alpha level of 5%, considering the actual accrual period of 64.5 months, and a minimum follow-up of 12 months. The power for the comparison between the arms when the difference in neurotoxicity is >30-50% is presented in Table 4.

Table 3. Calculated power and number of events required for detecting the compensating median PFS difference for >10-30% neurotoxicity

Comparison	**Patients**	**Median PFS difference**	**Hazard Ratio**	**Calculated power**	**Events required**
CapCar vs **F-Nal-Irl**	136 vs **68**	3.85 months (10.35 vs **6.5**)	0.63	92% (one-sided)	188
F-Nal-Irl vs *CapOX*	**68** vs *68*	3.85 months (*10.35* vs **6.5**)	0.63	83% (one-sided)	127
CapCar vs *CapOx*	136 vs *68*	3 months (9.5 vs *6.5*)	0.68	80% (one-sided)	190

*Power is calculated with a logrank test considering an actual accrual period of 64.5 months and a minimum follow-up of 12 months

Table 4. Calculated power and number of events required for detecting the compensating median PFS difference for >30-50% neurotoxicity

Comparison	**Patients**	**Median PFS difference**	**Hazard Ratio**	**Calculated power**	**Events required**
CapCar vs **F-Nal-Irl**	136 vs **68**	4.85 months (11.35 vs **6.5**)	0.57	98% (one-sided)	186
F-Nal-Irl vs *CapOX*	**68** vs *68*	4.85 months (*11.35* vs **6.5**)	0.57	92% (one-sided)	125
CapCar vs *CapOx*	136 vs *68*	4 months (10.5 vs *6.5*)	0.62	93% (one-sided)	187

*Power is calculated with a logrank test considering an actual accrual period of 64.5 months and a minimum follow-up of 12 months

Power calculations were performed in SAS, version 9.4.

Considering the numbers in Table 1 we will be able to investigate smaller differences in PFS, leading to more clinically relevant results.

Taking into account 15% withdrawal of patients from the trial before start of study medication, the total number to be included is 320.

3.4. What is the hypothesis testing framework for this study?

This study uses a superiority hypothesis testing framework for all primary and secondary outcomes.

3.5. Will interim analyses be performed in this study?

Interim safety analyses will be performed in the context of a formal data safety monitoring board as specified in the "Charter Data and Safety Monitoring Board (DSMB) investigator-initiated clinical research" for the LyRICX trial, version 1 date September 2018, approved by the data safety monitoring board on 13-09-2018 and stored in the trial master file. The interim analyses will be performed by an independent statistician not involved in any other aspect of the study employed by the Department of Epidemiology and Data Science of the Amsterdam University Medical Centre, The Netherlands.

3.6. When will the final statistical analysis of the study data be performed?

The statistical analyses of the primary and secondary outcomes will be performed when the last randomized patient has been followed for 12 months or when the minimum number of required events to achieve at least 80% power for all comparisons (Table 3) is reached earlier. In the latter case, the final analysis will take place when all randomized patients have had a minimum of 6 months of follow-up for sufficient observation of neurotoxicity. An update of the primary outcome analysis is planned to be performed 24 months after the last randomized patient.

3.7. At which time points are the outcomes measured and which "windows" are allowed?

All patients will undergo eligibility assessments within 14 days prior to starting study treatment.
CT thorax/abdomen should be made within 28 days prior to start of study treatment.
On day 1 of each chemotherapy cycle the following will be assessed:

- Adverse events according to CTCAE Version 5.0
- Concomitant medications
- Vital signs
- Weight
- ECOG/ WHO performance status
- Hemoglobin, platelet count, white blood cells (WBC) count, and neutrophils, lymphocytes, total bilirubin, direct bilirubin, AST/SGOT, ALT/SGPT, creatinine, ureum, LDH, CEA, CA 19.9. If patient receives nivolumab: TSH (and FT4 if applicable), glucose.
- Patient reported outcome measures: EORTC QLQ CIPN20 questionnaire (neuropathy) will be assessed every 3 weeks.

Every 9 weeks tumor evaluation will take place:

- Adverse events according to CTCAE Version 5.0
- Concomitant medications
- Vital signs
- Weight

- ECOG/ WHO performance status
- Hemoglobin, platelet count, white blood cells (WBC) count, and neutrophils, creatinine, sodium, potassium, calcium, chloride, phosphate, magnesium, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, yGT, AST/SGOT, ALT/SGPT, ureum, LDH, CEA, CA 19.9. If patient receives nivolumab: TSH (and FT4 if applicable), glucose.
- CT scan/ MRI scan for evaluation of tumor response
- Patient reported outcome measures (general): EQ-5D-5L, EORTC QLQ C30, EORTC QLQ OG25, happiness, HADS, WOPS, influence on work, use of healthcare.

There is a window of +/- 3 days allowed from the scheduled date for all visits and associated assessments.

See tables 13 and 14 in the protocol for a summary table of assessments per trial arm.

Section 4. Statistical Principles.

4.1. Which level or levels of statistical significance will be used in the study?

The primary outcome PFS will be viewed as significantly different between treatment arms if the one-sided p-values are less than 0.05. For all other analyses, two-sided tests with alpha 5% will be used.

4.2. Will the analysis adjust for multiplicity of statistical testing to ensure control of type I error rate?

The analysis will not adjust for multiplicity of statistical testing.

4.3. Which confidence intervals will be reported?

For the primary endpoint PFS, two-sided 90% confidence intervals (CI) will be presented. For all other parameters, two-sided 95% confidence intervals will be presented.

4.4. How is compliance defined and assessed?

Compliance to the randomised treatment is defined as minimum one cycle of the randomised treatment regimen.

4.5. How will compliance be presented?

Compliance will be presented as the percentage of all randomized patients that are in the per-protocol population.

4.6. What are defined as protocol deviations in this study?

Major protocol deviations are defined as violations from the study protocol which jeopardize the safety of the subject or the validity of the trial:

- No signed informed consent prior to registration
- Not all assessments done prior to randomisation to determine eligibility
- Ineligible subjects who were assigned treatment
    - No adenocarcinoma of the stomach or oesophagus
    - Metastatic disease not proven with histology or cytology
    - Prior (definitive/therapeutic) systemic therapy for irresectable or metastatic disease
    - No RECIST 1.1 measurable disease, including no CT scan of diagnostic quality done
    - Incorrect stratification at randomisation
    - Complete DPD deficiency
    - HER2 positive without contraindication Trastuzumab

- Baseline tumor assessment > 28 days before start treatment
- Tumor assessments that are missed or extremely out of window (>14 days)
- Tumor assessments not evaluated per RECIST 1.1 criteria (i.e. other modality used)
- Subject used concurrent anti-cancer treatment

All other deviations from the study protocol are minor protocol deviations.

Major protocol deviations can also classify as Serious Breaches, which are defined as any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial and/or data reliability and robustness to a significant degree in a clinical trial. See also the *"LyRICX standard operating procedure (SOP) Serious Breaches"* for more detail.

4.7. How will protocol deviations be presented in the reporting of this study?

Major protocol deviations and serious breaches will be line-listed according to treatment group. In addition, the number and percentage of patients in each treatment group experiencing one or more major protocol deviation or serious breach will be presented.

4.8. Which analysis populations will be defined?

'As randomised' analyses:

- **Intention-to-treat population:** includes all randomised patients, analysed according to their assigned treatment group, regardless of the treatment actually received.
- **Modified intention-to-treat population:** includes all randomised patients who started any of the three treatment regimens, analysed according to their assigned treatment group, regardless of the treatment received. Randomised patients that did not start any of the three treatment regimens are excluded.

'As treated' analyses:

- **Safety population:** includes all randomised patients who started with one of the three treatment regimens, analysed according to the treatment actually received. Randomised patients who did not start any first-line treatment are excluded.
- **Per protocol population:** includes only randomised patients who started their assigned treatment regimen. Randomised patients who did not receive any treatment, or who started a different treatment than assigned, are excluded.
- **Stric per protocol:** includes only randomised patients who met all eligibility criteria at randomisation and who started their assigned treatment. Patients who did not meet all eligibility criteria but were inadvertently randomised, or who did not start their assigned treatment, will be excluded.

Section 5. Study populations.

5.1. Which data were collected from participants, who were screened for eligibility for inclusion in the study, and how will these data be presented in study reports?

All patients that provided informed consent for screening are registered in the study.
Data collected from registered participants that were not randomised (screenings failures):

- Date written informed consent obtained
- Eligibility criteria that were not met
- Reason why the patient was not randomised (ineligible / subject withdrawal /clinical detoriation / other)

The number of screened patients and the reasons why they were not randomised will be presented in study reports.

5.2. What are the inclusion and exclusion criteria for the study?

Patients with histologically confirmed metastatic or irresectable HER2 negative adenocarcinoma of the stomach or oesophagus, not pre-treated with systemic therapy for irresectable or metastatic disease, and with measurable disease as assessed by RECIST 1.1 are eligible. Detailed inclusion and exclusion criteria are presented in section 4.1 and 4.2 in the protocol.

5.3. Which information will be presented in the flow chart for this study?

The mock-up of the CONSORT flow diagram is presented in the appendix to this statistical analysis plan.

5.4. What is the expected level of, timing of and reasons for withdrawal from the intervention and/or from follow-up and how will this be presented in the study reports?

We expect 15% of patients to withdraw from the study before start of study treatment due to clinical deterioration. Additionally, some patients will not have a response evaluation because of clinical deterioration and/or death before this time. Since the primary outcome is progression free survival, defined as time from randomization to progression or death, patients who withdraw before start of study medication are expected to have an event and will be analysed in the intention-to-treat population. Therefore, they will also be taken into account in the calculation of the percentage of neurotoxicity which is also part of the primary outcome (for the intention-to-treat analysis).

5.5. Which baseline characteristics of participants will be presented?

- Age in years
- Sex
- BMI in kg/m2
- ECOG performance status: 0,1,2,3,4

- Recurrent or primary metastatic disease
- Site of primary tumor: Oesophagus, Cardia or gastro-oesophageal junction, Stomach, Other
- (Predominant) histology: intestinal, diffuse, mixed, nos, unknown
- Differentiation grade: Well differentiated/low grade, Moderately differentiated / intermediate grade, Poorly or undifferentiated / high grade, Unknown or not done
- PD-L1 CPS: <5, ≥5, Not done
- Sites of disease: Primary tumor, Lymph nodes, Lung, Liver, Bone, Brain, Skin, Soft tissue, Ascites, Pleural effusion, Other
- Number of sites of disease: 1, 2, >2

A mock-up of the baseline characteristic table is presented in the appendix to this statistical analysis plan.

5.6. How will the baseline characteristics be summarized?

Categorical baseline characteristics will be summarized by presenting the number and percentage in each category. Continuous, normally distributed variables will be summarized by presenting the mean and standard deviation. Continuous, non-normally distributed variables will be summarized by presenting the median and interquartile range. As this is a randomized clinical trial, we will not statistically test for differences between treatment groups on baseline characteristics.

Section 6. Analysis.

6.1. How are the outcomes of this study defined?

The primary outcomes are progression free survival (PFS) 1 and neurotoxicity. These endpoints will be analysed separately, but study conclusions will be based on both endpoints.

- Progression free survival 1 is defined as the time from randomization, until the first moment of disease progression according to RECIST 1.1 criteria or death, whichever occurs first, censoring patients without progression and still alive
- Neurotoxicity is defined as grade 2-4 according to the NCI CTCAE version 5.0 as assessed by the treating physician of the following AE terms: Peripheral motor neuropathy, peripheral sensory neuropathy, paraesthesia, tendon reflex decreased, nervous system disorders-other. Only the worst event per patient will be counted.

The secondary outcomes are:

- Progression free survival 2: in case of reintroduction of study treatment after progression, progression free survival 2 is the time until progression or death (whichever occurs first) after this reintroduction. In case of start of second line treatment after progression, the time from start second line treatment until discontinuation of second line, progression or death (whichever occurs first) is taken as progression free survival 2. Patients are censored when still alive, without progression after reintroduction of study treatment or start second line treatment and when still continuing second line treatment.
- Overall survival: time from randomization to death or to last known to be alive.
- Response rate according to RECIST 1.1. Response is defined as best overall response: patients with a complete response or partial response according to RECIST 1.1 as best overall response.
- Adverse events according to NCI CTCAE version 5.0.
- Patient reported outcomes as assessed by the following questionnaires: EQ-5D-5L, EORTC QLQ C30, EORTC QLQ OG25, EORTC QLQ CIPN20, HADS, WOPS, Happiness, influence on work, use of healthcare.
- Percentage of patients proceeding to subsequent lines of treatment after progression and the types of subsequent treatments.
- Reasons for forgoing subsequent treatment after progression
- The primary and secondary endpoints for patients treated with and without nivolumab

6.2. Will any calculations or transformations be used to derive any outcome from the original data?

No

6.3. What analysis method will be used and how will the treatment effects be presented?

All analyses will be performed for the intention-to-treat population, modified intention-to-treat population, safety population and per protocol population, as defined in section 4.8.

Primary analyses:

- PFS curves will be constructed by means of the Kaplan Meier method and depicted in a graph including number of patients at risk in each arm at each timepoint. Comparisons of PFS curves will be performed by means of the stratified (stratification factors: ECOG (WHO) performance score, presence of liver metastases and having recurrent versus primary metastatic disease) log rank test. Each arm will be compared to the other arm according to comparisons described in Table 3 and Table 4 (CapCar versus F-Nal-IRI,

CapCar versus CapOx, and CapOx versus F-Nal-IRI). In addition, the median PFS will be reported per treatment arm along with the two-sided 90% CI. A stratified (stratification factors: ECOG (WHO) performance score, presence of liver metastases and having recurrent versus primary metastatic disease) Cox regression analysis will be performed to calculate the Hazard Ratio (HR) for the comparisons CapCar versus F-Nal-IRI, CapCar versus CapOx, and CapOx versus F-Nal-IRI. HR's will be reported with two-sided 90% CI's.

- Neurotoxicity grade 2-4 will be presented as percentage per treatment arm and compared using the Fisher's exact test. Comparisons will be performed for CapCar versus F-Nal-IRI, CapCar versus CapOx, and CapOx versus F-Nal-IRI. Only the worst event for each patient will be described. For the decision strategy in determining the best treatment, the p-value for the comparison between the arms in neurotoxicity grade will not be considered. In addition, a patient listing of neurotoxicity adverse events will be presented. This listing includes patient ID, randomized study arm, received treatment, adverse event, start- and end date, duration, severity, relatedness, action taken, and whether it is still ongoing.

Secondary analyses:

- PFS 2 curves will be constructed by means of the Kaplan Meier method. Analysis of PFS 2 will be similar to PFS, except that two-sided 95% CI's will be reported for the median PFS 2 and HR's.
- Overall survival curves will be constructed by means of the Kaplan Meier method. Analysis of OS will be similar to PFS, except that two-sided 95% CI's will be reported for the median OS and HR's for OS.
- Response rates will be presented as percentage of patients that achieved a complete or partial response as best overall response per treatment arm and compared using the Fisher's exact test. The two-sided 95% CI will be presented as well. Comparisons will be performed for CapCar versus F-Nal-IRI, CapCar versus CapOx, and CapOx versus F-Nal-IRI.
- Adverse events (AE) according to CTCAE version 5.0 will be categorized per system organ class, and percentages of any grade AE, ≥ grade 3 AE, Serious AE, treatment-related based AE on investigator's assessment will be presented per treatment arm. In addition, patient listings of (serious) adverse events will be presented. These listings include patient ID, randomized study arm, received treatment, (serious) adverse event, start- and end date, duration, severity, relatedness, action taken, and whether it is still ongoing
- In first instance, the mean score, standard error and 95% confidence interval on the 3 scales (sensory, motor, autonomic) of the EORTC QLQ CIPN20 questionnaire will be presented per time point and per treatment arm for the patients still alive at that time point. The means scores will also be plotted over time. Further analyses of patient reported outcomes will be specified in an addendum to this plan.
- Percentage of patients proceeding to subsequent lines of treatment after progression will be compared using Fisher's exact test. The types of subsequent treatments will be presented as counts and percentages. The two-sided 95% CI's will be presented as well. Comparisons will be performed for CapCar versus F-Nal-IRI, CapCar versus CapOx, and CapOx versus F-Nal-IRI.
- Reasons for forgoing subsequent treatment will be categorized, presented as counts and percentages per arm.

6.4. Will any assumptions for statistical methods be checked?

Normality of baseline variables will be assessed by visual inspection of histograms and q-q plots. Continuous baseline variables judged to follow a non-normal distribution will be summarized using medians and interquartile ranges.

6.5. Will sensitivity analyses be performed?

All analyses will be performed for the intention-to-treat population, modified intention-to-treat population, safety population and per protocol population, as defined in section 4.8. The

intention-to-treat analysis is considered the primary analysis whereas the analyses for the other analysis populations can be interpreted as sensitivity analyses.

6.6. Will subgroup analyses be performed?

We will perform sub-group analyses for all primary and secondary outcomes in patients treated with and without Nivolumab separately.

6.7. How will missing data be reported in the study reports and handled in the statistical analysis?

For the primary outcome PFS and secondary outcomes PFS2 and OS, patients without any events will be censored at last date known to be alive or without events.

For the primary outcome neurotoxicity: if patients with a neurotoxic adverse event have a missing grade, we will assume that these patients had 2-4 grade neurotoxicity.

For patients with a missing response, we will assume the worst possible outcome (no complete or partial response) for the secondary outcome response rate. The number and percentage of missing responses will be presented per treatment arm.

For the secondary outcomes percentage of patients proceeding to subsequent lines of treatment after progression and reasons for forgoing subsequent treatment, the number and percentage of missing data will be presented per treatment arm. For these outcomes, missing data will not be imputed.

For the patient reported outcomes (questionnaires), missing values will be imputed as appropriate.

6.8. Will additional analyses on the primary or secondary outcomes be performed?

No additional analyses will be performed on the primary or secondary outcomes.

6.9. How will harms be reported?

We will present line listing of all adverse events as assessed by CTCAE version 5.0. These listings include patient ID, randomized study arm, received treatment, (serious) adverse event, start- and end date, duration, severity, relatedness, action taken, and whether it is still ongoing

6.10. Which statistical software will be used to carry out the statistical analyses?

All statistical analyses will be performed in Rstudio version 24.12.1+563 (2024.12.1+563)

Section 7. References.

7.1. What is the title, date and version number of the current data management plan?
The current data management plan has the title “Data Management Plan LyRICX”, version number 2.0, dated 31-01-2022 and is stored in the trial master file.
7.2. What is the title, date and version number of the current data validation and derivation plan?
The current data validation and derivation plan has the title LyRICX data validatieplan Castor Protocol 5.0 version 2.0, is dated 05-12-2025 and is stored in the trial master file.
7.3. Where is the study master file stored?
The trial master file is stored physically at the trial office medical oncology at the AmsterdamUMC, location VUMC.
7.4. Where are the syntax files for data extraction, manipulation and preparation and statistical analysis stored?
The syntax files for data extraction, manipulation and preparation and statistical analysis are stored at the location K:\Upper GI – Slokdarm Maag \ LyRICX.
7.5. Which standard operating procedures will be adhered to when using and analysing data from this study?
When using and analysing data from the LyRICX trial, researchers will adhere to the Amsterdam UMC standard operating procedure RDM001 Research data management.
7.6. Which reporting guidelines will be adhered to when reporting on this study?
When reporting the results of this randomized clinical trial, the researchers will adhere to the SAMPL and CONSORT reporting guidelines.

Section 8. Appendix.

Additional Tables, Figures and Documents.

Figure 1. The CONSORT 2010 flow diagram of patients enrolled in the LyRICX trial.

Table 1. The baseline characteristics table of patients randomized in the LyRICX trial

Figure 1. LyRICX CONSORT 2010 Flow Diagram

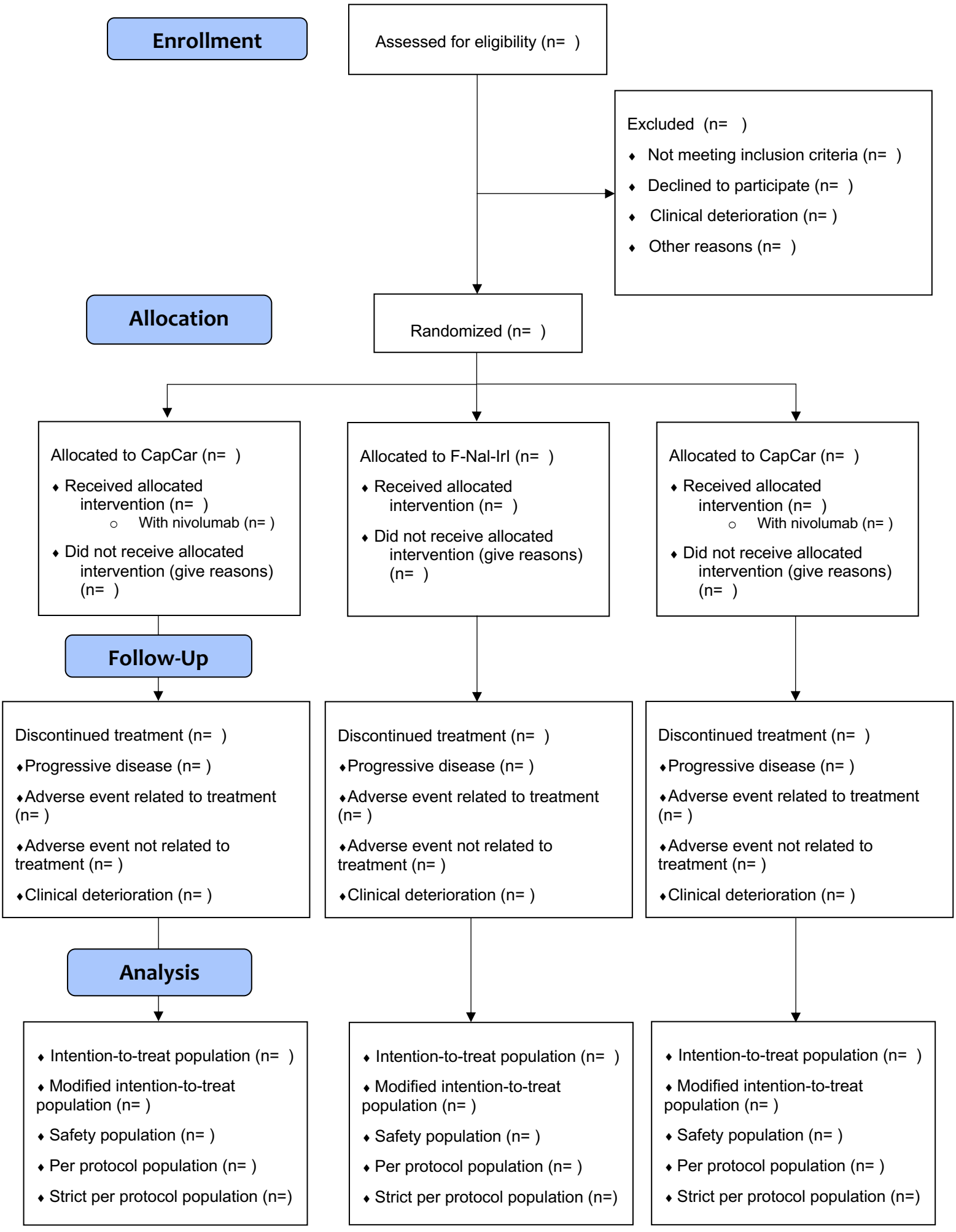

Table 1. The baseline characteristics table of patients randomized in the LyRICX trial

	All patients (n=)	F-Nal-Irl (n=)	CapCar (n=)	CapOx (n=)
Age				
Sex				
Male				
Female				
BMI				
ECOG performance status				
0				
1				
2				
3				
4				
Recurrent disease				
Primary metastatic disease				
Site of primary tumor				
Oesophagus				
Cardia or gastro-oesophageal junction				
Stomach				
Other				
(Predominant) histology				
Intestinal				
Diffuse				
Mixed				
Nos				
Unknown				
Differentiation grade				
Well differentiated/low grade				
Moderately differentiated / intermediate grade				

Poorly or undifferentiated / high grade
Unknown or not done
CPS
<5
≥ 5
Not done
Sites of disease
Primary tumor
Lymph nodes
Lung
Liver
Bone
Brain
Skin
Soft tissue
Ascites
Pleural effusion
Other
Number of sites of disease
1
2
>2