Statistical analysis plan

Study : Liver Transplantation in Patients With Unresectable Colorectal Metastases Treated by Chemotherapy TRANSMET

NCT 02597348

Date: January 16, 2024

Version: 1

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1. Preamble

The statistical analysis of the 'TRANSMET' study will be conducted in accordance with the analysis plan outlined below.

The analysis plan, drafted by the statistician, will be shared for review and validation with the principal coordinating investigator, the scientific coordinator, and the methodologist.

This plan will be implemented on the basis of a locked database.

The study involves patients with definitively unresectable colorectal liver metastases showing partial response or stability post-chemotherapy.

2. Study objectives

2.1. Primary objective

The objective is to compare the 5-year overall survival of patients receiving chemotherapy followed by liver transplantation (C + LT) to that of patients receiving chemotherapy alone (C)

2.2. Secondary objectives

- Compare overall survival at 3 years between the two arms.
- Compare progression-free survival at 3 years and 5 years between the two arms.
- Evaluate recurrence-free survival at 3 years and 5 years in arm C + LT.
- Evaluate the recurrence rate at 3 years and 5 years in arm C + LT.
- Compare the quality of life between the two arms.

3. Definition of the study populations

3.1. Description of protocol deviations

The protocol deviations described below will be discussed during a data review meeting with the investigator to define major discrepancies and minor discrepancies:

- Non-compliance with inclusion and/or exclusion criteria.

- Non-adherence to the treatment defined by randomization:
  - For patients randomized to arm C+LT:
    - Time between the last chemotherapy cycle and LT ≥ 3 months (major discrepancie).
    - Patient transplanted with progression on the pre-LT CT scan (major discrepancie).
    - Patient not transplanted (major discrepancie).
  - For patient randomized to arm C:
    - Patient who did not receive chemotherapy (major discrepancie).
    - Patient who underwent LT or resection (major discrepancie).

- Variables necessary for primary and secondary outcome criteria not provided:
  - Vital status or information on patient recurrence or progression is missing as of the last update.
  - Patient deceased with an undisclosed date of death.
  - Recurrence or progression occurred, but the date is not specified.
  - Visit date is not provided even though the visit took place.
  - Quality of life questionnaire not completed.

- Deviations from scheduled protocol visits: Visit not conducted as scheduled in the protocol.

- Deviations from protocol-specified timelines:
  - Delay exceeding 6 months between screening and inclusion.
  - No imaging results (MRI, CT scan, PET scan) from within the last 2 months before inclusion.

- Premature study discontinuation.

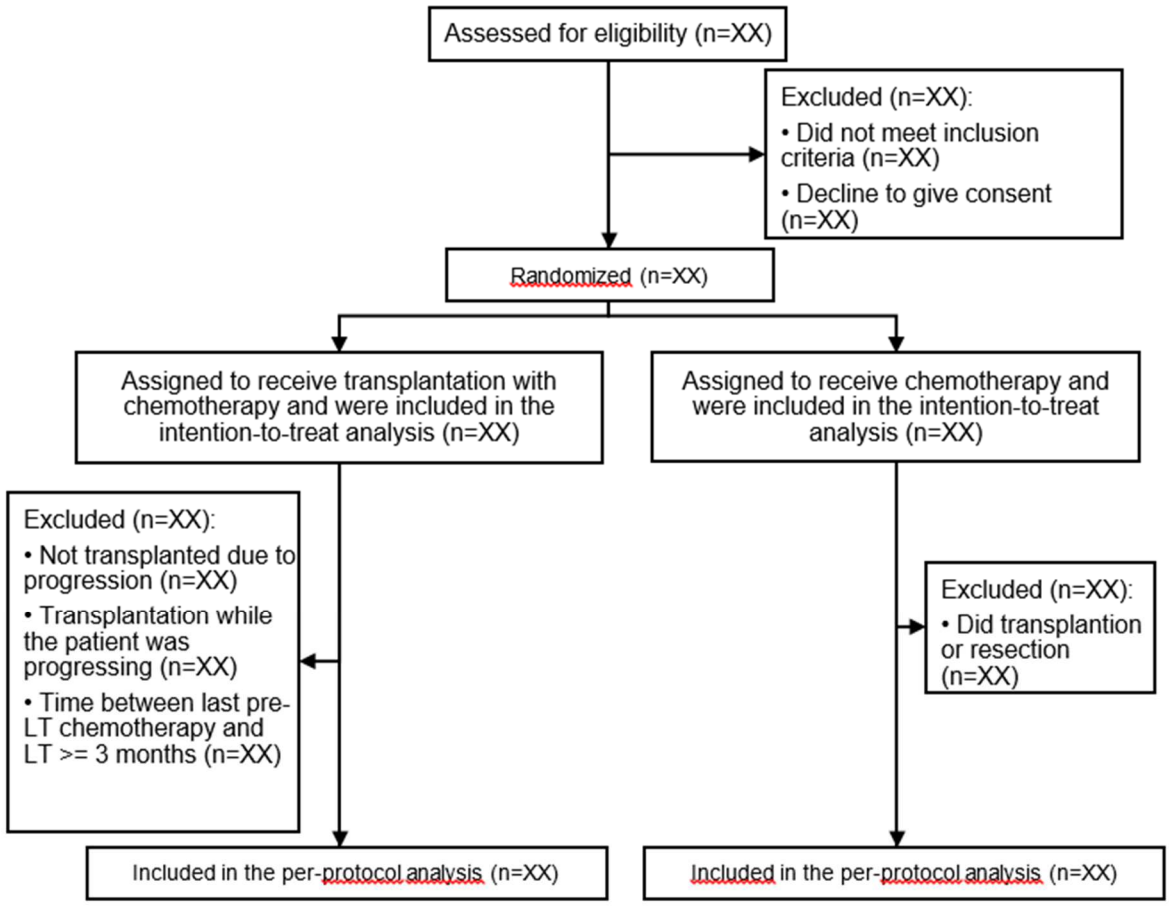
3.2. Descriptions of populations

Several populations will be considered in the analysis:

- **Patients selected by the local committee to be evaluated for inclusion**: This population consists of patients who have signed a consent, whether preliminary or final.
- **Enrolled patients:** This population comprises patients who have signed a final consent and are considered eligible by the validation committee. It includes properly enrolled patients (meeting all inclusion criteria and not meeting any exclusion criteria) and incorrectly enrolled patients (having at least one deviation from inclusion or exclusion criteria).
- **Intention-to-treat population (ITT):** This population consists of enrolled and randomized patients. All patients are evaluated in the arm to which they were assigned.
- **Per-protocol population (PP):** This population comprises patients who have fully adhered to the study protocol without major protocol deviations.

3.3. Flowchart

The following flowchart will be created :



4. Outcome measures

The analyses on overall survival will be conducted in the ITT population.

4.1. Primary outcome measure

The primary outcome is the 5-year overall survival. The time to overall survival is defined as follows:

- If the patient dies before the cut-off date*: Time between randomization and the patient's death, regardless of the cause.
- If the patient is alive at the cut-off date*: Time between randomization and the date of the last update**.

The maximum follow-up time is equal to the randomization date + 5 years, i.e., 60 months.

*The cut-off date is the date at which the data will be frozen. **The date of the last update can correspond to a visit date, a date of completion of the quality of life questionnaire, a start or end date of treatment, or an inter-cycle assessment date.

4.2. Secondary outcome measures

4.2.1. 3-Year overall survival

The 3-year overall survival is defined similarly to the primary outcome but at 3 years. The analysis will be conducted in the ITT population.

4.2.2.Comparison of progression-free survival at 3 and 5 years

In Arm C, progression is defined as the first progression occurring after randomization. In Arm C+LT, progression is defined as the first recurrence occurring after liver transplantation (LT).

The progression-free survival at 3 years is defined as follows:

- If the disease progresses one or more times before the cut-off date, and the first progression occurs within 3 years post-randomization: Time between randomization and the occurrence of the first progression.
- If the patient dies before the cut-off date without experiencing progression, and the death occurs within 3 years post-randomization: Time between randomization and death, regardless of the cause.
- If the patient is alive without progression at the cut-off date: Time between randomization and the date of the last update. The last update date will be a maximum of 3 years post-randomization.

The progression-free survival at 5 years is defined similarly but at 5 years. The analysis will be conducted in the PP population.

4.2.3. Recurrence-free survival at 3 et 5 years in arm C+LT

The recurrence-free survival at 3 years is defined as follows:

- If the patient experiences one or more recurrences before the cut-off date, and the first recurrence occurs within 3 years post-randomization: Time between randomization and the occurrence of the first recurrence.
- If the patient dies before the cut-off date without experiencing recurrence, and the death occurs within 3 years post-randomization: Time between randomization and death, regardless of the cause.
- If the patient is alive without recurrence at the cut-off date: Time between randomization and the date of the last update. The last update date will be a maximum of 3 years post-randomization.

The recurrence-free survival at 5 years is defined similarly but at 5 years. The analysis will be conducted in patients randomized to Arm C+LT and who underwent LT.

4.2.4. Recurrence rate at 3 et 5 years in arm C+LT

Recurrence at 3 years is defined as the occurrence of any recurrence, regardless of the site, within 3 years post-randomization. Recurrence at 5 years is defined as the occurrence of any recurrence, regardless of the site, within 5 years post-randomization. The analysis will be conducted in patients who underwent LT.

4.2.5.Quality of life

Two questionnaires, QLQ-C30 and QLQ-LMC21, are completed in both arms. A third questionnaire, NIDDK, is completed only in arm C+LT.

5. Description

5.1. Patients characteristics at the time of Colorectal Liver Metastases (CRLM) diagnosis

Description of characteristics by randomization arm. This analysis will include all patients from the ITT population.

5.2. Characteristics at the inclusion

Description of characteristics at enrolment by randomization arm. The analysis will include all patients from the ITT population.

5.3. Recipient and donor characteristics at LT

This analysis will focus on patients who underwent LT.

5.4. Type of recurrence and treatments in arm C+LT

The analysis will focus on patients who underwent liver transplantation (LT). Only the first recurrence will be described.

5.5. Treatments received in arm C post randomization

The analysis will focus on patients randomized to arm C and who had at least one post-randomization visit.

5.6. Tolerance

The toxicity of chemotherapy, the occurrence of adverse events and the complications occurring within 3 months post-LT will be described.

6. Statistical aspect

6.1. Description

Quantitative variables will be described using the mean, standard deviation, minimum, maximum, median, first quartile, and third quartile. Qualitative or categorical variables will be described using frequencies and percentages.

6.2. Comparison of characteristics at randomization

The patient characteristics at randomization will be compared using the Student's t-test or Wilcoxon-Mann-Whitney test for quantitative variables and the chi-squared test or Fisher's exact test for qualitative variables.

6.3. Primary analysis

The evaluation of overall survival will be conducted by constructing survival curves using the Kaplan-Meier method. Graphs will be created following the best practices defined by Pocock[3].

- If the proportionality of hazards is respected: Survival in each randomization arm will be compared using the Log-Rank test. The hazard ratio and the associated 95% confidence interval will be estimated using a Cox proportional hazards model.
- If the proportionality of hazards is not respected: the difference in Restricted Mean Survival Time (RMST) between the arms and the associated 95% confidence interval will be estimated.

The randomization stratification by cluster of centers will not be taken into account in the analyses. This is because it was done for administrative reasons.

6.4. Secondary analyses

- The comparison of overall survival at 3 years will be conducted using the same method as for the primary objective. The Kaplan-Meier curve will not be redrawn (refer to the Kaplan-Meier curve of the primary objective).

- The comparison of progression-free survival at 3 and 5 years will be conducted using the same method as for the primary objective.

- The evaluation recurrence-free survival at 3 and 5 years will be conducted by constructing survival curves using the Kaplan-Meier method. No comparison will be made.

- The recurrence rate will be described at 3 and 5 years. It will be calculated using the Kaplan-Meier method.

- Quality of life will be compared between randomization arms using a repeated measures model if the data allow.

6.5. Sensitivity analyses

In the PP population :
A sensitivity analysis for the primary endpoint will be conducted in the Per-Protocol population, using the same method as for the primary analysis. If the proportionality of hazards is not respected in the ITT analysis while it is in the PP analysis (or vice versa), the result will be expressed in terms of the difference in RMST for both analyses.

Additionally, an analysis adjusted for predictive factors of death may be conducted if the sample sizes permit. Potential risk factors for death include: KRAS mutation, Fong Clinical score >2 at inclusion, ACE at inclusion > 80 ng/mL, time interval between primary surgery and randomization > 12 months or > 24 months, and number of chemotherapy lines at inclusion >= 2.

In the ITT population :
A sensitivity analysis for the primary endpoint will be conducted in the ITT population in case of non-proportional hazards. It will be performed using a piecewise exponential model. Moreover, an analysis adjusted for predictive factors of death may be conducted if these factors are not balanced between randomization arms.

6.6. Imputation

When a date is incomplete because only the day is missing, it will be imputed to the 15th of the month.

For the variable 'number of CRLM in quantitative form, regardless of the evaluation time, the following imputation will be performed: When the number in the category is strictly greater than 20, the number of nodules in quantitative form is uncountable. The number of nodules in quantitative form is then imputed as 25. This imputation will be done even in the case where a specific number of nodules is provided and that number is strictly greater than 25.

For the variables 'number of CRLM at inclusion', 'diameter of the largest CRLM at inclusion', 'Fong score at inclusion', the following imputation will be performed: The information is that provided at the last evaluation before randomization. When this data is not available, the information taken into account is that provided at the inclusion CT scan, and failing that, at the inclusion MRI.

For the ACE and CA19-9 markers at inclusion, the following imputation will be performed: The information is that provided at the last evaluation before randomization. When this data is not available, the information taken into account is that provided at inclusion.

For the ACE and CA19-9 markers at D0, the following imputation will be performed: The information is that provided at D0. When this data is not available, the information taken into account is that provided during the last assay in the month preceding transplantation.

Patients in arm C+LT who have undergone transplantation and have the chemotherapy type = NA are considered as not receiving adjuvant chemotherapy.

7. Interim analyses

No interim analysis is planned in this study

8. Sample size

The number of required events is 29. It aims to demonstrate a 40% difference in overall 5-year survival between the two randomization arms (50% for arm C+LT versus 10% for arm C) with a power of 90%, a two-sided alpha of 5%, and a follow-up loss rate of 2% and 10% in the C+LT and C arms, respectively. When we noticed that some patients in the C+LT arm did not receive LT, we re-estimated the number of events to 50 assuming that patients without LT would have a 10% survival rate and that patients with LT would have a 50% survival rate.

9. Statistical report

At the conclusion of the analysis, all results will be compiled and statistically interpreted by the statistician in a statistical report, which will be validated by the principal coordinating investigator, the scientific coordinator

10. Planning

The statistical analysis plan must be written and validated before the database is frozen.

11. Bibliography

1 : Fong Y & al.. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230:309-321.

2 : Hagness M & al. Liver transplantation for non-resectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800-806.

3 : Pocock SJ & al. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet, 2002;359 :1686-1689.