MICROWAVE ABLATION VERSUS STEREOTACTIC BODY RADIOTHERAPY FOR COLORECTAL LIVER METASTASES IN OLIGOMETASTATIC DISEASE (LAVA-CRLM): A PROSPECTIVE, RANDOMISED, PHASE 2 TRIAL

NCT03654131

STATISTICAL ANALYSIS PLAN

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1. Introduction

1.1. Background

In colorectal cancer patients with oligometastatic disease (CRLM), resection of metastases is the treatment of choice and has been shown to increase overall survival (OS) [1]. However, resection is often not chosen for technical or medical reasons. Patients who are not eligible for resection can be considered for percutaneous microwave ablation (MW-ablation) or stereotactic body radiation therapy (SBRT) [2].

MW-ablation is considered the standard method among non-surgical modalities for ablation of liver metastases, and it has provided excellent local control rates for intermediate-sized CRLM (3-5 cm) with local control rates between 22%-90% depending on the study and tumor characteristics [3]. However, as a non-surgical but invasive method, it has limitations related to the size and location of the target lesions.

Stereotactic body radiotherapy (SBRT) is a non-invasive technique based on high-precision high-dose radiotherapy suitable for treatment of small targets in the body. SBRT has proven effective to gain tumor control with reported local control rates of 80% after 3 years [4]. SBRT performed on a MR-guided accelerator is the only non-invasive method to treat liver metastases.

No randomized studies exist comparing clinical results from MW-ablation and SBRT. With this trial we wanted to investigate the difference, if any, in local lesion progression after SBRT compared to MW-ablation in patients with colorectal liver metastases sized ≤4.0 cm.

1.2. Study Design

The LAVA-CRLM study is a randomized phase II trial between MW-ablation and SBRT – two standard treatment modalities for colorectal patients with metastatic disease in the liver for whom surgery is not considered the first choice of treatment by the multidisciplinary team. Patients will be randomized 1:1 (no stratification) between

Treatment arm A: MW-ablation
Treatment arm B: SBRT

The study will assess time to local lesion progression and is designed to have the ability to detect large differences in efficacy between the trial arms. In the absence of such large differences in efficacy, the study will for the first time provide descriptions of toxicity profiles in comparable populations treated with the two modalities and provide input to the design and feasibility of larger phase III trials.

1.3. Study Aims

1. To investigate SBRT as an alternative to percutaneous MW-ablation in patients with colorectal liver metastases sized ≤4.0 cm found eligible for percutaneous thermo-ablation as first choice of treatment by the local multidisciplinary team; evaluated through

freedom from local lesion progression
2. To evaluate the toxicity profiles of SBRT and MW-ablation
3. To establish prognostic factors for patients with colorectal liver metastases undergoing MW-ablation or SBRT

1.4. Sample size and expected accrual

It is assumed that freedom from local lesion progression in one trial arm is 94% after one year in one arm and 85% after one year in the comparing arm, corresponding to a hazard ratio of 0.38 between trial arms. It is assumed that patients are accrued over three years with one year additional follow-up and a median time to event of 4 years. Assuming exponential distribution of the hazard function, a sample size of 35 patients will yield a power of ~80% to observe such difference with an associated type I error of 5%. We plan accrual of **50 patients per arm** to account for loss of patients to competing causes and to account for intention to treat analysis of patients crossing over.

The study was designed with the explicit acknowledgement that the difference between the trial arms may likely be smaller than assumed. Consequently, the primary trial reporting will also focus on descriptive statistics of toxicity (in addition to local lesion control), as these represent unique contemporary data, especially for SBRT. (For comparison, some of the best data available on SBRT is a single institutional retrospective series published in the leading radiotherapy journal in 2017 with 70 patients [5].)

1.5. Planned analyses

1.5.1. Interim analysis

No interim analyses for the primary endpoint have been planned or conducted. Acute toxicity (secondary endpoint) has been reported as an at ASCO 2025 abstract, focusing on treatment allocation, compliance and toxicity profiles [6].

1.5.2. Final analysis

The final analysis will be conducted by the designated trial statistician once all randomised patients have reached one year of follow-up for the primary endpoint (local lesion control), and once data cleaning has been completed. The Statistical Analysis Plan (SAP) will be signed off by the primary investigator prior to database download and study unblinding for the trial statistician.

The primary endpoint analysis report will report on all study endpoints (primary and secondary). A final report (also reporting on all study endpoints) will be produced once all study patients are 5 years post-randomisation.

2. Endpoints

2.1. Primary endpoint

Freedom from local lesion progression

2.1.1. Secondary endpoints

- Overall survival
- Grade ≥3 toxicity in conjunction with treatment
    - Any grade 3 or above toxicity potentially associated with the treatment (within 1 months of study treatment completion)
- Toxicity profile
    - For the full study follow up period

2.2. Definitions and Derivations of Endpoints

2.2.1. Primary endpoint definition and evaluation

Local lesion progression is defined as the time from randomization to progression in a treated lesion (evaluated on the patient-level). All patients are followed using standard follow-up programmes for patients with liver metastases from colorectal cancer: CT imaging with contrast (assuming no contraindications) of the pelvis / abdomen every 3 months for the first two years, every 6 months for the subsequent two years, and with a final CT at the fifth year.

All treated lesions are evaluated for response tumor response or recurrence according to RECIST 1.1 criteria; with local lesion progression is defined as >20% increase in the longest diameter and minimum 5 mm increase, talking as reference the smallest longest diameter recorded since the treatment started. Progression in any treated lesion is counted as a local lesion progression event.

2.2.2. Primary endpoint estimand

An event will be defined as any local progression in a treated lesion, as described above.

Intercurrent censoring events will be

- Death (for any reason)
- End of imaging-based follow up for liver metastases control; either due to completion of standard follow up programme, referral to end of life care, or patient preference

The following events will not be considered censoring for evaluation of the primary endpoint

- New lesion in the liver
- New lesion outside of the liver
- Progression in any non-treated lesion (within or outside of the liver)
- Change in or initiation of new systemic treatment

Patients not receiving any local treatment will be managed through the principal stratum (i.e. the analysis population (mITT) for the primary endpoint).

2.2.3. Secondary endpoints

Overall survival

Overall survival (OS) is defined as the time from randomisation to the date of death from any cause. If an individual is lost to follow-up (albeit very unlikely) or alive at the time of analysis, they will be censored at the last date known to be alive. Minimum follow-up is 1 year.

Grade ≥3 toxicity in conjunction with treatment

Toxicity is clinician evaluated, using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0; at baseline, during treatment and up to five years post-treatment. Any grade 3 or above toxicity potentially associated with the treatment, within 1 months of study treatment completion, will be reported. Separate CTCAE items will be reported on their own, with event numbers split on arms.

Toxicity profile

The overall toxicity profile will be characterised by toxicity reporting throughout the study period (during treatment and up to five years post-treatment). Toxicity will be clinician evaluated, using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Any observed toxicity grade ≥2 will count as an event for the primary analysis, but all toxicity grades will be reported. Patients will be censored at death or at last follow-up (last clinical visit with study assessment); the latter may include referral out of the study follow-up programme (e.g. patient preference, referral to palliative services / end of life care, or other).

2.3. Missing data

Efforts will be made to retrieve missing data via a thorough data cleaning process. Missing data will be monitored and chased until either received, confirmed not available, or the trial is in analysis stage from 01/01/2026. For the primary endpoint analysis, missing outcome data will be handled through censoring. For overall survival analysis, no missing data is anticipated (as status of all patients can be sought through national registries). For toxicity endpoints, missing data will be reported; if substantial data is missing, an update to the statistical analysis plan may be considered to further describe how this may be handled in the analysis.

3. Populations

3.1. Modified Intention-to-treat population

The primary analysis population will be the modified intention-to-treat population (mITT). This will consist of all patients randomised, but excluding screening failures (i.e. not fulfilling inclusion / exclusion criteria) and patients who were unable to start any local study treatment (MWA or SBRT) due to disease progression (locally or distantly) or patient choice (e.g. preference for surgery). Patients will be analysed based on the arm they were randomised to, irrespective of the treatment received.

3.2. Per protocol population

The per protocol population will include only patients who received the full study treatment to which they were allocated (for SBRT arm patients, those who received all planned treatment fractions).

3.3. Safety Population

The safety population will consist of all patients randomised who started trial treatment (e.g. at least one fraction of SBRT); and evaluated based on the treatment received.

4. Data Analysis

4.1. General calculations and considerations

The patient population will be described in the form of patient and disease characteristics, using summary statistics. For continuous data, summary statistics will be presented as means with corresponding standard deviations and medians with inter-quartile ranges. For discrete data, summary statistics will include raw participant numbers and corresponding population percentages. All summaries will be presented overall and by treatment arm. All percentages will be calculated using the total number of participants within the appropriate population as the denominator (i.e. including all participants with missing data for that variable).

Percentages, means, medians and ranges will be reported to 1 decimal place. Standard deviations, parameter estimates and confidence intervals will be summarised to 2 decimal places. P-values will be rounded to 3 decimal places. Where appropriate, numeric values will be presented with 95% confidence intervals.

All statistical models presented will be assessed for appropriateness depending on the distribution of the data. Additionally, suitable diagnostic checks will be performed to check the underlying assumptions of the model / statistical method chosen.

Any secondary endpoint analyses that include hypothesis testing are not formally powered. It should therefore be recognised that any statistical significance might be due to chance. For such reasons, the results will be interpreted in combination with other relevant data and all subsequent inferences approached with caution.

4.2. Participant summary

The following patient numbers and information will be presented in a CONSORT flow diagram

- Randomised
- Allocated each treatment arm
- Patients excluded from the mITT population
- Received each treatment (and reasons for not receiving study treatment / crossing over)
- Lost to follow-up and withdrawals (and reasons why)
- Analysed in the mITT population
- Analysed in the per protocol population
- Analysed in the safety population

4.2.1. Baseline Characteristics

Baseline patient and clinical data recorded will be tabulated using frequencies and summary statistics. This will include an overview of systemic treatments received during study follow up.

4.3. Primary endpoint analysis

The primary endpoint will be analysed based on the mITT population. Number of events in each arm will be reported, as well as the number of patients censured during the study follow-up. Additionally, the number of individual lesion failures will be reported. Potential follow-up time will be assessed using the inverse Kaplan-Meier estimator.

Freedom from local lesion progression will be estimated in each arm using Kaplan-Meier estimators, with 95% confidence intervals, and local lesion control at 1 year reported in each arm (with corresponding confidence intervals). Treatment arms will be compared using the log-rank test, and the corresponding p-value reported. The hazard ratio between the arms (and its 95% confidence interval) will be estimated using a Cox-regression model, with treatment arm as the sole covariate.

A secondary analysis will use the per protocol population, following the same principles as above.

4.4. Secondary endpoint analysis

Overall survival will be estimated in each arm using the Kaplan-Meier estimator. Survival at 1 and 3 years will be reported in each arm, with corresponding 95% confidence intervals. Treatment arms will be compared using the log-rank test, and the corresponding p-value reported. The hazard ratio between the arms (and its 95% confidence interval) will be estimated using a Cox-regression model, with treatment arm as the sole covariate. As for the primary endpoint, the analysis will be based on the mITT population, with secondary analyses using the per protocol population.

All toxicity analyses will be conducted on the safety population. For toxicity in conjunction with treatment, the number and proportion of grade ≥3 events in each arm will be reported; providing both the total number of patients with grade ≥3 events as well events split on types. The proportion of patients with grade ≥3 events in each arm will be compared with Fisher's exact test. A full listing of all toxicity events (split on arm, types, and grade) will also be produced.

The toxicity profile will be evaluated by the cumulative incidence of any treatment-related grade ≥2 toxicity in each arm, using the Aalen–Johansen estimator. Any differences between the arms will be assessed using Fine-Gray regression to estimate the sub-distribution hazard ratio for treatment arm; reporting the hazard ratio with its 95% confidence interval as well as the corresponding p-value. Time will be calculated from date of randomization, and death will be considered a competing risk. A full listing of all toxicity events (split on arm, types, and grade) at any time during follow-up will also be produced.

4.5. Explorative endpoint analysis

Additional explorative analyses will be conducted; reflecting the prospective data collected on the study.

In particular, patient reported outcome measures have been collected, using the EORTC QLQ-C30 questionnaire. These will be evaluated as overall quality-of-life as well as domain-specific symptoms and functioning scores over time, in accordance with the standard EORTC manuals. Treatment arms may be compared using mixed effects linear regression.

Lesion-specific local control will be estimated by evaluating each treated lesion separately; and treatment arms compared using random effects Cox regression (with patient as a random effect).

5. References

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