STARLET

Statistical Analysis Plan

A prospective individual patient data meta-analysis of randomised controlled trials in EGFR mutant NSCLC with brain metastases to assess the effect of SRS + Osimertinib compared to Osimertinib alone on intracranial progression free survival at 12 months. (STARLET)

Robledo KP, *et al. BMJ Open* 2024; 14:e078335. doi: 10.1136/bmjopen-2023-078335

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1 Administration

1.1 Trial registration number

Registry Name	Prospero
Trial Identifying number	CRD42022330532 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=330532)
Date of registration	5 June 2022

1.2 Protocol

The protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for protocols (PRISMA-P) (1).

The protocol has been submitted for publication to BMJ Open. A link to the publication will be provided here once it is available.

1.3 Version history

SAP version	Date	Changes made	Authors
0.1	August 2023	First draft created	Kristy Robledo, Yu Yang Soon
0.2	December 2023	Updates following team meeting in November	Kristy Robledo, Yu Yang Soon
1.0	30 January 2024	Feedback following input from team (Cheryl Ho, Shilo Lefresne, Chee Lee)	Kristy Robledo, Yu Yang Soon

1.4 Contributors to the statistical analysis plan

This statistical analysis plan has been prepared based on Australian Clinical Trials Alliance templates and JAMA guidelines, with additional review of PRISMA guidelines for IPD-MA.

Name	Affiliation	Role on study	SAP contribution
Kristy Robledo	NHMRC CTC	Statistician	Created first draft
Yu Yang Soon	National University Hospital	Trial Chair (OUTRUN)	Commented and contributed to first draft
Fiona Hegi-Johnson	Peter MacCallum Cancer Centre	Trial Chair (OUTRUN)	Commented and contributed to first version
Chee Khoon Lee	NHMRC CTC	Trial Chair (OUTRUN)	Commented and contributed to first version
Ivan Weng Keong Tham	National University Hospital	Trial Chair (OUTRUN)	Reviewed and approved
Ross Soo	National University Hospital	Trial Chair (OUTRUN)	Reviewed and approved
Cheryl Ho	BC Cancer	Trial Chair (LUOSICNS)	Commented and contributed to first version
Shilo Lefresne	BC Cancer	Trial Chair (LUOSICNS)	Commented and contributed to first version

1.5 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention(s) being assessed).

Dr Fiona Hegi-Johnson	Trial Radiation Oncology Chair (OUTRUN)	Fiona Hegi-Johnson Digitally signed by Fiona Hegi-Johnson Date: 2024.02.23 10:32:29 +11'00' Fiona Hegi-Johnson
A/Prof Chee Khoon Lee	Trial Medical Oncology Chair (OUTRUN)	Chee Khoon Lee Digitally signed by Chee Khoon Lee Date: 2024.02.21 16:47:48 +11'00' Chee Lee
Dr Shilo Lefresne	Trial Radiation Oncology Chair (LUOSICNS)	Shilo Lefresne Digitally signed by Shilo Lefresne Date: 2024.02.21 06:06:41 -08'00' Shilo Lefresne
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Dr Kristy Robledo	Trial Statistician	Kristy Robledo Digitally signed by Kristy Robledo Date: 2024.02.16 13:55:39 +11'00' Kristy Robledo

2 Study synopsis

Design	Prospective Individual participant data (IPD) meta-analysis (MA)
Participants	*EGFR* mutant NSCLC with brain metastases diagnosed de novo or developed while on first line *EGFR* TKIs first or second line setting.
Intervention and Comparator	**Osimertinib versus Stereotactic radiosurgery (SRS) + Osimertinib** **Osimertinib**: an oral, potent, selective, irreversible inhibitor of both *EGFR-TKI* sensitising and resistance mutations in NSCLC with a significant selectivity margin over wild-type *EGFR*. Osimertinib will be administered orally as one 80 mg tablet once a day. A cycle of treatment is defined as 28 days of once daily Osimertinib treatment. Treatment with Osimertinib will commence following randomisation. Participants may continue to receive treatment with Osimertinib as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of any of the listed discontinuation criteria. **Stereotactic radiosurgery (SRS)**: a specialised radiation technique in which sophisticated technology is used to deliver large radiation doses to small targets, potentially up to 40mm in size. SRS is planned after randomisation. Standard therapy with Osimertinib 80 mg will be taken once daily commencing after the completion of SRS.
Outcome	**Primary outcome:** Intracranial progression free survival (ic-PFS) at 12 months as measured by RANO-BM criteria Secondary outcomes: • Ic-PFS,Extracranial Progression free survival (ec-PFS), • overall survival, • time to salvage whole brain radiotherapy, • time to salvage SRS, • time to local brain failure, • time to distant brain failure, • QOL (QLQ-C30 and QLQ-BN 20), • Adverse events of interest (eg. Radionecrosis)
Countries of recruitment	Australia, Singapore and Canada at the time of the writing of this analysis plan
Subgroups	Biomarker status: Exon 19 deletion versus Exon 21 L858R versus rare sensitizing mutations, pending numbers Line of therapy: first vs second

Number of brain metastases: Either <4 vs 4 or more or 1 versus more than 1, pending total numbers
Diameter of largest lesion: =<15mm vs >15mm
Age at baseline: <70 vs >=70 years
Gender: male vs female
Country of treatment: Singapore vs Australia vs Canada
Ethnicity: Asian vs other
Smoker: never versus ex/current smoker
Extracranial disease at baseline : present vs absent
ECOG: 0 versus >=1

2.1 Eligibility criteria

2.1.1 Types of studies

STARLET will include RCTs only. Randomisation may occur at the individual level or by cluster and quasi-randomised trials will be excluded. There are no language or date restrictions.

2.1.2 Trial participants

Participants will be eligible if they are receiving Osimertinib in the first- or second-line setting. For those receiving Osimertinib as first line systemic therapy, all newly diagnosed participants must have a documented sensitising EGFR mutation (including exon 19 del, L858R (exon 21), and rare sensitizing mutations: G719X (exon 18), L861G (exon 21), S768I (exon 20) and T790M (exon 20)) and intracranial metastasis, with or without extracranial disease. For those receiving Osimertinib as second line systemic therapy, participants will have developed intracranial metastases while on first-line 1st or 2nd generation EGFR TKI therapy, with no or stable extracranial disease regardless of T790M mutation.

Intracranial disease is defined as: (a) ≤ 10 lesions visible and measurable on protocol screening MRI, with at least one BM amenable to SRS; (b) no single BM exceeding 30mm in longest diameter; and (c) absence of neurologic symptoms except for headache, nausea or seizure which were medically controlled.

2.1.3 Interventions

One intervention is SRS followed by Osimertinib. The SRS dose-fractionation schedule depends on size and location of the lesion. The SRS is to be planned after randomisation, and Osimertinib commences after the completion of SRS. Osimertinib treatment is described below.

The other intervention is Osimertinib alone. Osimertinib will be administered orally as one 80 mg tablet once a day. A cycle of treatment is defined as 28 days of once daily Osimertinib treatment.

For those allocated to Osimertinib alone, treatment with Osimertinib will commence following randomisation. Participants may continue to receive treatment with Osimertinib as long as they are continuing to show clinical benefit, as judged by the treating clinician, and within the guidelines of the relevant trial protocol's discontinuation criteria.

2.2 Information sources and search strategy

We searched the following databases from their inception: Medline (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCO), PsychInfo, ClinicalTrials.gov and the World Health Organisation's International Clinical Trials Registry Platform's Search Portal. The full

search strategy is available in Appendix 1. The initial search was completed up to July 2023, and will be updated regularly to search for new trials until end-2023. Collaborators and contacts were asked to notify us of any additional planned, or ongoing completed trials that may fulfil eligibility criteria. In July 2023, only the two trials (OUTRUN: NCT03497767 and LUOSICNS: NCT03769103) have been identified, and both trial teams have agreed to share IPD for this collaboration.

2.2.1 Selection of studies for inclusion in the review

Two members of the STARLET Collaboration (KPR and YYS) will independently screen all future retrieved records against eligibility criteria. Any discrepancies will be resolved by consensus or, if required, adjudication by a third reviewer. The Principal Investigator and/or corresponding author of any additional eligible studies will be invited to join the STARLET Collaboration. If there is no response to initial emails, we will contact other co-authors or contacts listed on registration records. If IPD are not available for an eligible trial, we will use aggregate data where possible.

2.3 Data collection, management, and confidentiality

2.3.1 Data receipt / extraction

De-identified IPD will be shared via secure data transfer platforms or via institutional secure email using password-protected zip files. Data will be provided according to a pre-specified coding template where possible, otherwise, data will be accepted in any format and recoded as necessary. The data management team will receive and store the data in perpetuity in a secure, customised database at the NHMRC Clinical Trials Centre, University of Sydney, and data management will follow the University of Sydney's Data Management Policies. Each trial team will also be asked to provide metadata (such as questionnaires, data collection forms, and data dictionaries) to aid understanding of the datasets. Trial-level data, such as intervention details (setting, timing and duration), intervention details, method of sequence generation, allocation concealment, geographical location, sample size, outcome measures and definitions will be cross-checked against published reports, trial protocols, registration records and data collection sheets, in order to ensure data integrity.

2.3.2 Data processing

IPD from each trial will be checked with respect to range, internal consistency, consistency with published reports and missing items. Integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of participant characteristics across intervention and control groups. Any inconsistencies or missing data will be discussed with trialists/data managers and resolved by consensus. Each included trial will be analysed individually, and results shared with trialists for verification. Once finalised, data from each of the trials will be combined into a single database.

2.3.3 Risk of bias assessment and certainty of evidence appraisal

Included studies will be assessed for risk of bias by two reviewers, independently, using the criteria described in the Cochrane handbook (2): random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (3). Any differences will be resolved by consensus or with a third reviewer.

2.4 Outcomes

The primary outcome will be ic-PFS at 12 months, as determined by RANO-BM criteria (4). All outcomes and their definitions are in Table 1, with full definitions given later in this analysis plan.

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Table 1: Outcomes for individual patient data meta-analysis

Outcome	
Primary outcome	Intracranial progression free survival (ic-PFS) at 12 months
Secondary outcomes	ic-PFS (intracranial progression free survival)
	ec-PFS (extracranial progression free survival)
	Overall survival
	Time to salvage whole brain radiotherapy
	Time to salvage SRS
	time to local brain failure
	time to distant brain failure
	Health related quality of life: QLQ-C30 and QLQ-BN 20
	Adverse events of special interest

2.5 Subgroups

Individual and study-level subgroup analyses will be conducted for ic-PFS. Individual-level characteristics to be assessed include:

- mutation type (EGFR exon19 deletion vs exon 21 L858R vs uncommon sensitising mutations),
- line of therapy (first vs second),
- number of BM (either: <4 vs ≥4 or 1 vs ≥2, pending total numbers),
- diameter of largest lesion (≤15mm vs >15mm),
- age at baseline (<70 vs ≥70 years),
- sex (male vs female),
- country of treatment (Singapore vs Australia vs Canada),
- Patient reported race (Asian vs other),
- smoker (never vs ex or current smoker),
- extracranial disease presence at baseline (present vs absent),
- ECOG performance status (0 vs ≥1).

The number of participants within each subgroup, as well as the number of ic-PFS events, will be checked to be sufficient for the pre-specified subgroup analyses prior to any analyses. Otherwise, categories will be reassessed prior to any subgroup analyses being performed, by consensus of the STARLET collaboration.

3 Statistical principles

3.1 General principles

3.1.1 Estimand definition

As per ICH E9(R1)2, a precise definition of the relevant estimand for each of the efficacy objectives requires the specification of: (1) the treatment; (2) population of interest; (3) the endpoint; (4) handling of other intercurrent events; and, (5) the population-level summary measure used to compare treatments. The standard estimand definition for the efficacy objectives is based on the following specifications:

1. the treatment conditions of interest are randomisation to Osimertinib compared to SRS plus Osimertinib;

2. the population of interest is that defined by the protocol inclusion/exclusion criteria;

3. the endpoints are as per the definitions in Section 4;

4. a 'treatment policy' approach will be used to account for intercurrent events (ie. intention to treat analyses); and,

5. the population-level summary measures used to compare treatments are as per the definitions in Section 4

For the primary outcome, the endpoint is the difference in the intracranial progression free survival at 12 months, measured by the difference between the pooled Kaplan-Meier estimates from the trials (Osimertinib minus SRS plus Osimertinib).

3.1.2 Interim analyses

There are no formal interim analyses.

3.1.3 Timing of final analysis

The final analysis of the primary outcome will be performed after all patients randomised either reach 12 months of follow-up, are censored, or progress. Given the last patient was randomised in the April 2023, we anticipate that data syntheses and analyses will commence around first quarter 2024.

Other secondary outcomes will be analysed at the same time.

3.1.4 Multiplicity

There will be no formal adjustments to any confidence intervals for multiplicity. However, we will follow Schulz and Grimes' approach (5) and interpret the patterns and consistency of results across related outcomes rather than focusing on statistical significance alone.

3.1.5 Missing data

Main analyses will be based upon available data. Missing data may be explored in sensitivity analyses using multiple imputation, for outcomes where missing data may be an issue (i.e. health related quality of life).

3.1.6 Analysis populations

All analyses given will be intention to treat, other than the safety analyses.

There are two main analysis populations:

3.1.6.1 Full analysis population

The full analysis set will include all eligible randomised participants. The full analysis set will be used for all analyses.

3.1.6.2 Safety analysis population

The safety analysis set will consist of all participants who received at least one dose of randomised treatment and for whom post dose data are available. Safety data will be summarised according to treatment received.

An exploratory analysis in the patients with evaluable disease at baseline may also be performed.

3.1.7 Adjudication of outcomes

There are no planned adjudication of any of the trial events.

3.1.8 Confidence intervals and p-values

All point estimates will be summarized with a 95% confidence interval. P-values will be calculated for outcomes.

4 Statistical Analyses

4.1 Integrity of data

The data from both trials will be checked prior to any analyses. These checks will include ranges, internal consistency, and consistency with any internal reports.

The integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of participant characteristics across intervention and control groups.

Any inconsistencies or missing data will be discussed with trialists/data managers and resolved by consensus. Each included trial will be analysed individually, and results shared with trialists for verification. Once finalised, data from each of the trials will be combined into a single database that will be used for the analyses documented here.

4.2 PRISMA flowchart

A PRISMA flowchart will be provided and summarise the trials screened, reasons not eligible, trials that agree to provide IPD.

In addition, participant level information such as the number randomized, number with 12 months of follow-up and number withdrawn may also be included.

4.3 Baseline characteristics

The following baseline characteristics will be given by treatment allocated:

- Age
- Gender
- Study site
- ECOG
- Smoking history
- History of NSCLCEGFR mutation
- Total number of brain metastases (both target and non-target)
- Largest brain metastases lesion size (mm)
- Largest brain metastases lesion size (=<15mm vs >15mm)
- Brain metastases at presentation (Newly diagnosed vs Developed on first line TKI)
- Neurosurgery treatment of brain metastases

4.4 Risk of bias assessment and certainty of evidence appraisal

Included studies will be assessed for risk of bias by two reviewers, independently, using the criteria described in the Cochrane handbook (2): random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (3). Any differences will be resolved by consensus or with a third reviewer.

A grade evidence profile will be given following the draft outline below.

4.5 Summary of study treatment

SRS completion can be defined as completion of the plan, partial completion or did not commence treatment.

Months on Osimertinib will be summarised as time between starting medication and reported end of medication, ignoring any changes in dosage.

4.6 Primary outcome

4.6.1 Definition of ic-PFS

ic-PFS is defined as time from randomisation to intracranial disease (ic) progression or death (from any cause). Intracranial progression is defined by RANO-BM criteria, given in Table 2 below. Patients who withdraw from the randomised therapy and receive further non-study anti-cancer therapy will be clinically reviewed (blinded to allocated treatment) to deem if they should be censored at the commencement of this therapy. If patients do not receive any other non-study therapy at study withdrawal, they will be followed-up for ic-PFS, and censored at the date of the last assessment.

Table 2: Response assessment criteria for brain metastases

	COMPLETE RESPONSE	PARTIAL RESPONSE	STABLE DISEASE	PROGRESSIVE DISEASE
Target lesions	None	≥ 30% decrease in sum longest distance relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum longest distance relative to nadir	≥ 20% increase in sum longest distance relative to nadir[b]
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease[b]
New lesion(s)[a]	None	None	None	Present[b]
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable[c]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse[b]
Requirement for response	**All**	**All**	**All**	**Any[c]**

a A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, such as due to its small size, continued therapy can be considered, and follow up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion.

b Progression occurs when this criterion is met.

c Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

4.6.2 Estimation of ic-PFS at 12 months

The estimation of the ic-PFS at 12 months will be using Kaplan-Meier estimates. The trials results will be pooled in a two-stage approach.

The ic-PFS-12 will be estimated using Kaplan-Meier estimates, with an estimate obtained for the Osimertinib and the SRS + Osimertinib arms, along with the corresponding standard error ($se(O)$ and $se(SRS)$ respectively)(6), for each trial. The difference between the treatment arms will then be obtained for each trial, along with the corresponding standard error of the difference. This is calculated using $\sqrt{se(O)^2 + se(SRS)^2}$, where $se(O)$ is the standard error of the Osimertinib estimate at 12 months and $se(SRS)$ is the standard error of SRS + Osimertinib at 12 months. The differences between the treatment arms for each trial (along with the corresponding standard errors of the difference) are then pooled using standard inverse variance weighting. Given we are interested in the treatment effect within these trials (conditional inference), a common effects model (fixed-effects) will be used (7).

The estimates for each treatment arm at 12 months and the difference between the treatment arms at 12 months will be reported for each trial. The pooled overall difference with its 95% CI will also be reported. Heterogeneity of this effect will be quantified using the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance.

4.6.3 Sensitivity analyses for the primary outcome

If any trials are eligible and do not consent to share IPD data, a sensitivity analysis will be conducted for the primary outcome; including published aggregate data combined with IPD.

If appropriate, contour-enhanced funnel plots to examine whether there are differences in results between more and less precise studies will be explored. If other trials are included retrospectively (eg. after the final analysis of that trial is performed), a sensitivity analysis will be performed comparing those results to the prospective trials.

4.7 Secondary outcomes with no competing risks

Estimates at 12 months will be given by Kaplan Meier methods and plots will be given by treatment arm and trial. Cox regression models will be performed to estimate the hazard ratio for treatment and its 95% CI, adjusted for trial. Treatment by trial interactions will be explored in each model.

4.7.1 IC-PFS

As defined above for the primary outcome.

4.7.2 EC-PFS

Extracranial progression is defined as the time from randomisation until progression according to RECIST, or death from any cause. Patients who withdraw from the randomised therapy and receive further non-study anti-cancer therapy will be clinically reviewed (blinded to allocated treatment) to deem if they should be censored at the commencement of this therapy. If patients do not receive any other non-study therapy at study withdrawal, they will be followed-up for ec-PFS and censored at the date of the last assessment.

4.7.3 Overall survival

Overall survival is defined as the time from the date of randomisation until death (from any cause). Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

4.8 Secondary outcomes with competing risks

These outcomes, detailed below, will be analysed using a one stage approach taking into account the relevant competing risks, by estimating the sub-distribution hazard ratio and its 95% CI using Fine-Gray regression. These models will adjust for trial, and treatment by trial interactions will be explored in each model.

Each of the outcomes below will have cumulative incidence plots by trial and randomized treatment arm given, as well as cumulative incidence plots by treatment only. Rates at 12 months will be provided with relevant 95% CI.

4.8.1 Salvage whole brain RT (WBRT) +/- neurosurgery

Use of salvage WBRT is defined as time from randomisation to start of salvage WBRT (+/- neurosurgery) with a competing risk of death. Any participant not known to have WBRT (+/- neurosurgery) or not known to have died at the time of the analysis will be censored at the last known time to have not received WBRT i.e. the last follow up visit where this was confirmed.

4.8.2 Salvage SRS

Salvage SRS is defined as the time from randomisation to the start of any additional SRS treatment, with the competing risk of death. For those patients randomised to SRS+Osimertnib, this is not the randomised SRS treatment, but any further SRS treatment subsequently given. Patients will be censored at the last known time not to have salvage SRS (i.e. the last follow-up visit that no treatment was confirmed).

4.8.3 Local brain failure (LBF)

LBF is measured as time from randomisation to LBF, defined as pre progression criteria detailed in Table 2 for existing lesions, with competing risks of distant brain failure (without concurrent local failure), extracranial progression or death with no documented progression. Any participant not known to have LBF, or not known to have distant brain failure, extracranial progression or death at

the time of analysis will be censored at the last known time not to have LBF (i.e. the last follow up visit where this was confirmed).

4.8.4 Distant brain failure (DBF)

DBF is measured as time from randomisation to DBF, defined as development of new brain lesions with competing risks of local brain failure (without concurrent distant brain failure), extracranial progression or death. Any participant not known to have DBF, or not known to have LBF, extracranial progression or death at the time of analysis will be censored at the last known time not to have DBF (i.e. the last follow up visit where this was confirmed).

4.9 Health related quality of life

Patient reported outcomes will be assessed using the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires. Outcome variables consisting of a score from 0 to 100 will be derived for each of the symptom scales / items and the functional scales of interest according to the EORTC QLQ-C30 and EORTC QLQ-BN20 scoring instructions.

The following functional scales will be calculated:

- Physical
- Role
- Emotional
- Cognitive
- Social

The following symptom scales will be calculated:

- Fatigue
- Nausea
- Pain
- Dyspnoea
- Insomnia
- Appetite loss
- Constipation
- Diarrhoea
- Financial difficulties

Higher scores on the functioning scales indicate better health status and function. Higher scores on the symptom scales indicate greater symptom burden.

An overall measure of global health will also be calculated.

From the QLQ-BN20, we will calculate:

- Future uncertainty,
- Visual Disorder,
- Motor Dysfunction,
- Concentration Difficulty
- Headaches,
- Seizures,
- Drowsiness,
- Hair loss,

- Itchy Skin,
- Leg Weakness,
- Bladder control

These scores will be summarised graphically over time by treatment.

4.9.1 Early versus late

The change in in HR-QOL from baseline will be summarised by treatment for early (6 months) versus late (12 months). The change at these two timepoints will be calculated for the scores given above. A clinically meaningful change of 10 points will be explored.

4.10 Deterioration free survival

Time from randomisation until the first instance of:

- 10-point deterioration from baseline in HR-QOL, without a subsequent 10 point or more improvement compared to baseline
- Discontinuation of Osimertinib treatment (regardless of SRS completion for O+SRS patients)
- Intracranial progression (either local or distant)
- Death from any cause

Participants with none of these events will be censored at the last known time to be progression free.

Two endpoints will be defined for deterioration free survival. One will look at cognitive deterioration, where the HR-QOL changes may be in either the cognitive function scale or the concentration difficulty scale. The other will look at global deterioration free survival, using the global health score. Treatment arms will be compared using hazard ratios for treatment obtained from cox regression models, adjusted for study. Kaplan Meier curves will also be produced.

4.11 Graphical summaries

Graphical summaries for presentation of the above analyses will be provided. These include, but are not limited to, swimmers, waterfall, and spider plots.

4.11.1 Swimmers plot

We will summarise in a plot, by trial and treatment, the ordering of the following events:

- local brain progression
- distant brain progression
- death
- extracranial disease progression
- salvage SRS
- salvage WBRT

4.11.2 Waterfall and spider plots

For these plots, patients with a post baseline RANO-BM assessment of target lesion diameters will be included. Reasons patients were not included (ie. died before reassessment) will be given.

For the spider plot, the change in the sum of the RANO-BM target lesion diameters from baseline will be plotted over time, by patient. For the waterfall plot, the maximum decrease in the sum of the RANO-BM target lesion diameters will be plotted for each patient. Plots by trial and treatment will be given.

Additionally, extracranial disease will be summarised in both spider and waterfall plots, using RECIST tumour measurements, by trial and treatment.

4.12 Subgroups

Differences in treatment effect between the pre-specified subgroups will be examined by fitting a treatment by subgroup interaction term within a Cox regression model for ic-PFS, taking into account competing risks. These models will be adjusted for trial.

The following subgroups will be explored, after an assessment has ensured there are enough participants and enough events for a hazard ratio to be estimated. Categories will be pooled prior to any analyses if required.

- mutation type (EGFR exon19 deletion vs exon 21 L858R vs uncommon sensitising mutations),
- line of therapy (first vs second),
- number of BM (either: <4 vs ≥4),
- diameter of largest lesion (≤15mm vs >15mm),
- age at baseline (<70 vs ≥70 years),
- sex (male vs female),
- country of treatment (Singapore vs Australia vs Canada),
- ethnicity (Asian vs other),
- smoker (never vs ex or current smoker),
- extracranial disease presence at baseline (present vs absent),
- ECOG performance status (0 vs ≥1).

Findings of subgroup analyses will be reported as exploratory.

4.13 Safety outcomes

Safety outcomes will be summarised for all patients that received at least one dose of treatment (see section 3.6.2 Safety analysis population). Adverse events and Serious Adverse Events (SAE) will be summarised by treatment for these patients, including by AE term and grade.

Additionally, Adverse events of interest will be summarised in a similar fashion, by AE term and grade. These include:

- Central nervous system necrosis (radiation necrosis)
- cognitive disturbance
- edema cerebral
- muscle weakness right sided
- muscle weakness left sided
- Fatigue
- Gait disturbance
- Headache
- Seizures

- Tremors
- Lethargy
- Dizziness
- Syncope
- Stroke
- Intracranial hemorrhage

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Table 3: GRADE Evidence profile for STARLET (example)

	Quality Assessment								
Outcome*	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	O	SRS+O	Hazard ratio (95% CI)	Quality of the evidence (GRADE)
Ic-PFS	Statement on if concerns are found	Statement on if concerns are found	Statement on if concerns are found	Statement on if concerns are found	Statement on if concerns are found	n/N (12 month event rate)	n/N (12 month event rate)		High/Moderate etc
(line for each outcome)									

*For the included two randomised controlled trials