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Protocol for a systematic review with prospective individual patient data meta-analysis in EGFR-mutant NSCLC with brain metastases to assess the effect of SRS+osimertinib compared to osimertinib alone: the STARLET Collaboration

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ABSTRACT

Background Patients with advanced non-small-cell lung cancer (NSCLC) with activating mutations in the epidermal growth factor receptor (*EGFR*) gene are a heterogeneous population who often develop brain metastases (BM). The optimal management of patients with asymptomatic brain metastases is unclear given the activity of newer-generation targeted therapies in the central nervous system. We present a protocol for an individual patient data (IPD) prospective meta-analysis to evaluate whether the addition of stereotactic radiosurgery (SRS) before osimertinib treatment will lead to better control of intracranial metastatic disease. This is a clinically relevant question that will inform practice.

Methods Randomised controlled trials will be eligible if they include participants with BM arising from *EGFR*-mutant NSCLC and suitable to receive osimertinib both in the first-line and second-line settings (P); comparisons of SRS followed by osimertinib versus osimertinib alone (I, C) and intracranial disease control included as an endpoint (O). Systematic searches of Medline (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCO), PsychInfo, ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform's Search Portal will be undertaken. An IPD meta-analysis will be performed using methodologies recommended by the Cochrane Collaboration. The primary outcome is intracranial progression-free survival, as determined by response assessment in neuro-oncology-BM criteria. Secondary outcomes include overall survival, time to whole brain radiotherapy, quality of life, and adverse events of special interest. Effect differences will be explored among prespecified subgroups.

Ethics and dissemination Approved by each trial's ethics committee. Results will be relevant to clinicians, researchers, policymakers and patients, and will be disseminated via publications, presentations and media releases.

Prospero registration CRD42022330532.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of an individual patient data (IPD) meta-analysis will give increased statistical power for the relative comparison of SRS followed by osimertinib versus osimertinib alone on intracranial progression-free survival. Such a meta-analysis will also enable the exploration of subgroups.

⇒ The frequency of outcome assessment and outcome measures may be collected and reported differently across included trials, which may lead to some imprecision. Harmonisation of clinical trial protocols through prospective meta-analysis will address some of these limitations.

⇒ A limitation of this study is that the searches will only be conducted until late 2023 and any studies that are registered after this time will not be included.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) with activating mutations in the epidermal growth factor receptor (*EGFR*) gene is a distinct subtype that is characterised by a high tumour response rate when treated with small-molecule *EGFR* tyrosine kinase

inhibitors (TKIs). Approximately 20%–40% of patients with advanced NSCLC will develop brain metastases (BM) at some point during their disease course, and it is possible that patients with *EGFR*-mutant NSCLC are at greater risk due to improved survival.[1 2]

Stereotactic radiosurgery (SRS) involves the precise delivery of high doses of ionising radiation over a single or limited number of fractions to an intracranial target.[3] Based on populations with BM from predominantly NSCLC but not enriched for *EGFR*, incorporating SRS in the management of BM was associated with improvement in overall survival (OS) for those with a single lesion and prolongation of functional independence in those with up to three BM.[4] However, the detrimental effects of whole brain radiation are now well known, such that SRS alone has become the standard of care. Use of SRS alone for multiple BM has been adopted routinely,[5] in particular, given the prospective Japanese observational study involving patients with up to 10 BM that demonstrated that the OS of patients with 5–10 BM treated with SRS alone was non-inferior to those with 2–4 BM.[6] Hence for patients with a good performance status, the American Society for Radiation Oncology (ASTRO) strongly recommends SRS for those with 1–4 BM and also conditionally recommends this treatment for those with 5–10 BM.[7]

Osimertinib is an oral, third-generation irreversible mutant-selective, wild-type sparing *EGFR* TKI with higher central nervous system penetration and intracranial activity than first-generation *EGFR* TKIs. It has been approved by the US Food and Drug Administration as a first-line treatment for *EGFR*-mutant NSCLC based on the FLAURA trial,[8 9] as well as a second-line treatment for those who have developed a T790M mutation after exposure to first-generation *EGFR* TKI based on the AURA3 trial.[10] In subset analyses, patients with stable, asymptomatic BM had significantly prolonged intracranial disease progression-free survival (ic-PFS) with osimertinib compared with geftinib or erlotinib in the FLAURA trial[11] and platinum-pemetrexed in the AURA3 trial.[12] However, the true intracranial activity of osimertinib remains unclear, as a significant number of patients enrolled in these trials had prior cranial radiotherapy (24% in FLAURA and 41% in AURA3). Notably, the OCEAN trial, a single-arm phase II study of T790M-positive *EGFR*-mutant NSCLC and untreated BM, found the intracranial response rate for second-line osimertinib was 67% and the median ic-PFS was 25 months.[13]

Currently, the optimal sequencing of SRS and osimertinib in patients with *EGFR*-mutant NSCLC and untreated BM is unclear. The joint guideline between the American Society of Clinical Oncology (ASCO), the Society for Neuro-Oncology (SNO), and ASTRO states that local therapy may be delayed in selective patients with asymptomatic BM from *EGFR*-mutant NSCLC; however, the strength of the recommendation is weak as the quality of evidence supporting this recommendation is low.[14] There is conflicting evidence from retrospective cohort studies. Magnuson and colleagues found that those who received upfront cranial irradiation had longer OS than those who received upfront first-generation *EGFR* TKI with deferred cranial irradiation.[15] Similarly, Yu and colleagues observed that upfront cranial radiotherapy was associated with reduced cumulative incidence of ic-PFS in the entire cohort receiving osimertinib and improvement in OS in a subset of patients with 1–3 BM.[16] However, Thomas and colleagues did not find any improvement.[17]

Two phase II randomised controlled trials (RCTs), OUTRUN (TROG 17.02)[18] and LUOSICNS[19] are independently recruiting participants with BM from *EGFR*-mutant NSCLC to evaluate whether SRS followed by osimertinib is more efficacious than osimertinib alone in delaying the progression of intracranial disease. OUTRUN completed recruitment in September 2022, and LUOSICNS completed recruitment in April 2023. Both have a sample size of 40 participants and individually lack the statistical power to formally compare treatment arms. They are hypothesis generating to inform the planning of a future, definitive, phase III RCT.

Therefore, we have developed a collaboration, oSimertinib with or without sTereotActic Radiosurgery in egfr non-small cell Lung cancEr with brain metastases (STARLET), to prospectively conduct an individual patient data (IPD) meta-analysis of these RCTs to compare the effects of SRS followed by osimertinib versus osimertinib alone followed by deferred local cranial therapies on intracranial disease control in patients with BM from *EGFR*-mutant NSCLC. The purpose is to establish which treatment strategy will lead to better control of intracranial disease, and if there are subgroups of patients that might benefit more from the combination treatment strategies.

METHODS AND ANALYSIS

A systematic review and IPD meta-analysis will be conducted according to the recommended methods.[20 21] Lead investigators of eligible RCTs will be invited to share their IPD and join this STARLET Collaboration. Eligible RCTs identified up to July 2022 are listed in online supplemental appendix 1. This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for protocols (PRISMA-P, checklist detailed in online supplemental appendix 2)[22] and has been registered on PROSPERO (CRD42022330532). If subsequent potentially eligible RCTs are published, a nested prospective meta-analysis may be used in order to combine the retrospective inclusion of these additional trials with the proposed results gained from these analyses. At this time, there are no consumers actively involved with the Collaboration.

Eligibility criteria

Types of studies

STARLET will include RCTs only. Randomisation may occur at the individual level or by cluster, however

quasi-randomised trials will be excluded. There are no language or date restrictions.

Trial participants

Participants will be eligible if they are receiving osimertinib in the first-line 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), 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 first or second-generation *EGFR* TKI therapy, with no or stable extracranial disease regardless of T790M mutation.

Intracranial disease is defined as (1) ≤10 lesions visible and measurable on protocol screening MRI, with at least one BM amenable to SRS; (2) no single BM exceeding 30 mm in longest diameter and (3) absence of neurological symptoms except for headache, nausea or seizure, which were medically controlled.

Interventions

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

The other intervention is osimertinib alone. Osimertinib will be administered orally as one 80 mg tablet per 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 continue to show clinical benefit, as judged by the treating clinician, and within the guidelines of the relevant trial protocol's discontinuation criteria.

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), ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform's Search Portal. The full search strategy is available in online supplemental appendix 1. The initial search was completed up to July 2022 and will be updated regularly to search for new trials until late-2023. Collaborators and contacts were asked to notify us of any additional planned or ongoing completed trials that may fulfil eligibility criteria. At this time, only the two aforementioned trials (OUTRUN, TROG 17.02: NCT03497767[18] and LUOSICNS: NCT03769103[19]) have been identified, and both trial teams have agreed to share data with this Collaboration.

Selection of studies for inclusion in the review

Two members of the STARLET Collaboration 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 coauthors or contacts listed on registration records. If IPD are not available for an eligible trial, we will use aggregate data where possible.

Data collection, management and confidentiality

Data receipt and extraction

Deidentified 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 prespecified 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 National Health and Medical Research Council (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), 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.

Data processing

IPD from each trial will be checked with respect to range, internal consistency, consistency with published reports and missing items. 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 will be shared with trialists for verification. Once finalised, data from each of the trials will be combined into a single database.

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,[23] 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

Table 1 Outcomes for individual patient data meta-analysis

Outcome	Definition
Primary outcome	
ic-PFS at 12 months	Kaplan-Meier estimate at 12 months. Time from randomisation to intracranial disease progression, as defined according to RANO-BM
Secondary outcomes	
ic-PFS	Time from randomisation to intracranial disease progression, as defined according to RANO-BM
ec-PFS	Time from randomisation to extracranial disease progression, as defined according to response evaluation criteria in solid tumours
PFS	Time from randomisation to any disease progression
Overall survival	Time from randomisation to death
Time to salvage whole-brain radiotherapy	Time from randomisation to salvage whole-brain radiotherapy
Time to salvage stereotactic radiosurgery	Time from randomisation to salvage stereotactic radiotherapy
Time to local brain failure	Time from randomisation to local brain failure
Time to distant progression	Time from randomisation to distant disease progression
Quality of life	EORTC QLQ for cancer (QLQ-C30). This is the core module of the QLQ suite.
	EORTC QLQ for brain neoplasm (QLQ-BN20). This is the brain tumour module.
Adverse events of special interest	Rates of the following adverse events (e.g.): radiation necrosis, neurocognitive impairment, oedema cerebral, muscle weakness right side, muscle weakness left side, fatigue, gait disturbance, headache, seizures, tremors, lethargy, dizziness, syncope, stroke and intracranial haemorrhage.

ec-PFS, etracranial progression-free survival; EORTC, European Organization for Research and Treatment of Cancer; ic-PFS, intracranial progression-free survival; QLQ, Quality of Life Questionnaire ; RANO, response assessment in neuro-oncology.

evaluation approach.[24] Any differences will be resolved by consensus or with a third reviewer.

Primary outcome

The primary outcome will be ic-PFS at 12 months, as determined by response assessment in neuro-oncology brain metastases (RANO-BM) criteria.[25]

Secondary outcomes

All outcomes and their definitions are detailed in table 1. Secondary outcomes include OS, time to whole brain radiotherapy, quality of life, and adverse events of special interest.

Covariates and subgroups

Individual and study-level subgroup analyses will be conducted for ic-PFS. Individual-level characteristics to be assessed include mutation type (*EGFR* exon 19 deletion vs exon 21 L858R vs uncommon sensitising mutations, pending numbers), line of therapy (first vs second), number of BM (either: <4 vs ≥4 or 1 vs ≥2, pending total numbers), diameter of the largest lesion (≤15 mm vs >15 mm), 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) and Eastern Cooperative Oncology Group performance status (0 vs ≥1). If the data are insufficient for the prespecified subgroup analyses, categories will be reassessed prior to any analyses, by consensus of the STARLET Collaboration.

Data analysis

A detailed statistical analysis plan was prepared and agreed on by the STARLET Collaboration prior to any analyses being undertaken (online supplemental appendix 3). Analyses will include all randomised participants who meet the inclusion criteria, for which IPD are available. All analyses will be based on randomised treatment allocation (intention to treat principle).

For the primary outcome of ic-PFS at 12 months, Kaplan-Meier estimates (with their variances) will be calculated from each of the trials and pooled using inverse variance weighting (two-stage approach). Other secondary outcomes will be examined using Cox regression or linear models, adjusted for study (one-stage approach). The heterogeneity of treatment effects across trials will be estimated using I^2 and investigated by fitting a trial-by-treatment interaction term to the models. Any heterogeneity identified will be explored further.

Differences in treatment effect between the prespecified subgroups will be examined by testing a subgroup-by-treatment interaction term within a Cox regression model for ic-PFS. The findings of subgroup analyses will be reported as exploratory.

Missing data may be explored in sensitivity analyses using multiple imputations. Analyses will be performed using SAS and the open-source software R.[26]

Assessment of selection or publication bias

Potential selection bias and publication bias may be investigated by conducting a nested prospective meta-analysis and comparing trials that were included prospectively versus those identified retrospectively in a sensitivity analysis (if appropriate). Contour-enhanced funnel plots

will be used to examine whether there are differences in results between more and less precise studies.

Adjustments for multiple tests

No formal adjustments will be made for multiple comparisons. However, we will follow the Schulz and Grimes' approach[27] and interpret the patterns and consistency of results across related outcomes rather than focusing on statistical significance alone.

Planned sensitivity analyses

If possible, the following sensitivity analyses will be conducted for the primary outcome, including published aggregate data combined with IPD in the meta-analysis compared with IPD alone, and including prospectively included trials only. Additional sensitivity analyses may be conducted on other outcomes to determine the effect of missing data. Sensitivity analyses are detailed in the statistical analysis plan.

Project management

Membership in the STARLET Collaboration includes representatives from the trials contributing IPD to the project. Trial representatives have the opportunity to contribute their expert knowledge to the collaboration and provide input into the protocols, statistical analysis plan and final results manuscript. The STARLET Collaboration will be responsible for data collection, management and analysis, as well as communication within the collaboration, including the organisation of virtual or face-to-face collaborator meetings.

Patient and public involvement

There was no formal patient or public involvement in this study design. We do not have identifying information on individual trial participants, but we plan to disseminate results to each site's principal investigators to distribute to their trial participants.

Ethics and dissemination

Ethical considerations

IPD will be provided by each included trial on the stipulation that ethical approval has been provided by their respective Human Research Ethics Committees (or equivalent), and participants gave informed consent before enrolment. Only trials with ethical approval will be included in these analyses. Trialists remain the custodians of their own data, which will be deidentified before being shared with the collaboration.

Publication policy

Manuscripts will be prepared by the relevant members of the STARLET Collaboration and circulated for comment, revision and approval prior to submission for publication. Any reports of the results from this study will be published either in the name of the collaborative group or by representatives of the collaborative group on behalf of the STARLET Collaboration, as agreed by all members.

DISCUSSION

An IPD meta-analysis is considered the gold standard of systematic reviews and has many advantages over a standard aggregate approach. This includes the collaboration of a range of expert trialists and biostatisticians in order to ensure that all possible RCTs are included and appropriate analysis of outcomes is performed. Through prospectively collaborating, STARLET can prespecify the patient population, interventions and outcomes clearly, and harmonise trial protocols where possible. Another clear advantage is the increase in statistical power. The two eligible RCTs identified at this time are both phase II RCTs that, individually, are not powered to identify a statistically significant difference between treatments, but rather are looking for efficacy signals and the safety of treatment.

We will seek to address this with the use of a prospective meta-analysis to include published aggregate data and by encouraging planned and ongoing trials to collect our core outcomes and share data.

Based on the recruitment timelines of the two trials identified, we plan to complete study identification by the end of 2023, IPD collection by mid-2024, and conduct the analyses and disseminate the results by mid-2025. These timelines may be adjusted if follow-up is completed early or if additional trials are identified and not completed in time to provide data.

The results of this systematic review will guide whether a phase III study is required to inform clinical practice and, if so, may help investigators preplan subgroup analyses of interest.

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Contributors KPR, CKL, YYS, FHJ, CH, AN and SL conceived the idea for this study. KPR, YYS, CKL, FHJ, MP, RS, CH, AN and SL developed the research question and protocol registration. KPR wrote the first draft of the manuscript. KPR and

YYS developed the eligibility and search strategy, and performed the search and screening. CKL, FHJ, CH, SL, AN, AS, MBP, RAS, BJS, IWKT, AP, MD, DBS, AGS, JT, CNL, WYK, YH, YLEA, JL, CY, MCL and APT provided critical review and feedback at each stage of the process. All authors critically reviewed and provided feedback on the intellectual content of the manuscript and agreed and approved the final version. KPR is the guarantor of the review.

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REFERENCES

1 Barnholtz-Sloan JS, Sloan AE, Davis FG, *et al*. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan detroit cancer surveillance system. *J Clin Oncol* 2004;22:2865–72.
2 Rangachari D, Yamaguchi N, VanderLaan PA, *et al*. Brain metastases in patients with EGFR-Mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer*2015;88:108–11.
3 Suh JH, Kotecha R, Chao ST, *et al*. Current approaches to the management of brain metastases. *Nat Rev Clin Oncol* 2020;17:279–99.
4 Andrews DW, Scott CB, Sperduto PW, *et al*. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665–72.
5 Sahgal A, Ruschin M, Ma L, *et al*. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. *Neuro Oncol* 2017;19:ii2–15.
6 Yamamoto M, Serizawa T, Shuto T, *et al*. Stereotactic radiosurgery for patients with multiple brain metastases (Jlgk0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387–95.
7 Gondi V, Bauman G, Bradfield L, *et al*. Radiation therapy for brain metastases: an ASTRO clinical practice guideline. *Pract Radiat Oncol* 2022;12:265–82.
8 Ramalingam SS, Vansteenkiste J, Planchard D, *et al*. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 2020;382:41–50.
9 Soria J-C, Ohe Y, Vansteenkiste J, *et al*. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med* 2018;378:113–25.
10 Mok TS, Wu Y-L, Ahn M-J, *et al*. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017;376:629–40.
11 Reungwetwattana T, Nakagawa K, Cho BC, *et al*. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non–small-cell lung cancer. *J Clin Oncol* 2018;36.
12 Wu Y-L, Yang JC-H, Kim D-W, *et al*. Phase II study of crizotinib in East Asian patients with Ros1-positive advanced non-small-cell lung cancer. *J Clin Oncol* 2018;36:1405–11.
13 Yamaguchi H, Wakuda K, Fukuda M, *et al*. A phase II study of osimertinib for radiotherapy-naive central nervous system metastasis from NSCLC: results for the T790m cohort of the OCEAN study (Logik1603/Wjog9116L). *J Thorac Oncol* 2021;16:2121–32.
14 Vogelbaum MA, Brown PD, Messersmith H, *et al*. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. *J Clin Oncol* 2022;40:492–516.
15 Magnuson WJ, Lester-Coll NH, Wu AJ, *et al*. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol* 2017;35:1070–7.
16 Yu F, Ni J, Zeng W, *et al*. Clinical value of upfront cranial radiation therapy in osimertinib-treated epidermal growth factor receptor-mutant non-small cell lung cancer with brain metastases. *Int J Radiat Oncol Biol Phys* 2021;111:804–15.
17 Thomas NJ, Myall NJ, Sun F, *et al*. Brain metastases in EGFR- and ALK-positive NSCLC: outcomes of central nervous system-penetrant tyrosine kinase inhibitors alone versus in combination with radiation. *J Thorac Oncol* 2022;17:116–29.
18 A randomised phase II trial of Osimertinib with or without SRS for EGFR Mutated NSCLC with brain metastases. 2024. Available: https://ClinicalTrials.gov/show/NCT03497767
19 Study of Osimertinib + SRS vs Osimertinib alone for brain metastases in EGFR positive patients with NSCLC. 2021. Available: https://ClinicalTrials.gov/show/NCT03769103
20 Seidler AL, Hunter KE, Cheyne S, *et al*. A guide to prospective meta-analysis. *BMJ* 2019;367:l5342.
21 TierneyJS, Clarke M. Chapter 26: individual participant data. *Cochrane Handb Syst Rev Interv ver* 2019;6.
22 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
23 HigginsJS, Page MJ, Elbers RG, *et al*. Cochrane handb syst rev interventions: cochrane. 2022.
24 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
25 Iuchi T, Shingyoji M, Sakaida T, *et al*. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer* 2013;82:282–7.
26 R Core Team. R: A language and environment for statistical computing. Vienna, Austria, 2022.
27 Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005;365:1591–5.

STARLET: Supplementary One

Search strategies

These searches were run on the 2nd April, 2024.

1 MEDLINE (OVID)

```
Ovid MEDLINE(R) ALL <1946 to March 29, 2024>

1     Carcinoma, Non-Small-Cell Lung/     74074
2     lung cancer.mp.   212008
3     (lung metast* or lung tumo* or lung carcinoma*).mp.   64188
4     1 or 2 or 3 261424
5     cerebral ventricle neoplasms/ or infratentorial neoplasms/ or
supratentorial neoplasms/     6918
6     (brain metast* or brain carcinom* or cerebral metast* or intracranial
metast*).mp.      20737
7     5 or 6      27534
8     ErbB Receptors/   48633
9     (egfr* or epidermal growth factor receptor*).mp.      110839
10    8 or 9      119248
11    4 and 7 and 10    1163
12    Protein Kinase Inhibitors/    59664
13    Antineoplastic Agents/  323913
14    (Osimertinib or Tagrisso or AZD9291).mp.  2988
15    12 or 13 or 14    369506
16    11 and 15   533
17    cranial irradiation/ or radiosurgery/ or radiotherapy, computer-
assisted/ or radiotherapy, high-energy/ or radiotherapy, image-guided/ or
x-ray therapy/    42630
18    radiosurg*.mp.    26840
19    (radioherap* or radiation or irradiation).mp.   813181
20    17 or 18 or 19    832422
21    16 and 20   132
22    randomized controlled trial.pt.     610373
23    controlled clinical trial.pt. 95519
24    randomized.ab.    640129
25    clinical trials as topic.sh.  201969
26    randomly.ab.      430224
27    trial.ti.   305931
28    22 or 23 or 24 or 25 or 26 or 27    1536139
29    exp animals/ not humans.sh.   5207954
30    28 not 29   1418586
31    21 and 30   20
32    Carcinoma, Non-Small-Cell Lung/     74074
33    lung cancer.mp.   212008
34    (lung metast* or lung tumo* or lung carcinoma*).mp.   64188
35    32 or 33 or 34    261424
```

```
36    cerebral ventricle neoplasms/ or infratentorial neoplasms/ or
supratentorial neoplasms/     6918
37    (brain metast* or brain carcinom* or cerebral metast* or intracranial
metast*).mp.      20737
38    36 or 37    27534
39    ErbB Receptors/   48633
40    (egfr* or epidermal growth factor receptor*).mp.      110839
41    39 or 40    119248
42    35 and 38 and 41  1163
43    Protein Kinase Inhibitors/    59664
44    Antineoplastic Agents/  323913
45    (Osimertinib or Tagrisso or AZD9291).mp.  2988
46    43 or 44 or 45    369506
47    42 and 46   533
48    cranial irradiation/ or radiosurgery/ or radiotherapy, computer-
assisted/ or radiotherapy, high-energy/ or radiotherapy, image-guided/ or
x-ray therapy/    42630
49    radiosurg*.mp.    26840
50    (radioherap* or radiation or irradiation).mp.   813181
51    48 or 49 or 50    832422
52    47 and 51   132
53    randomized controlled trial.pt.     610373
54    controlled clinical trial.pt. 95519
55    randomized.ab.    640129
56    clinical trials as topic.sh.  201969
57    randomly.ab.      430224
58    trial.ti.   305931
59    53 or 54 or 55 or 56 or 57 or 58    1536139
60    exp animals/ not humans.sh.   5207954
61    59 not 60   1418586
62    52 and 61   20
```

20 trials found

2 Embase (OVID)

The same search strategy for Medline (OVID) given above was run in Embase (OVID).

```
Embase Classic+Embase <1947 to 2024 March 29>

1     Carcinoma, Non-Small-Cell Lung/  78994
2     lung cancer.mp.  424757
3     (lung metast* or lung tumo* or lung carcinoma*).mp.    237026
4     1 or 2 or 3     582902
5     cerebral ventricle neoplasms/ or infratentorial neoplasms/ or
supratentorial neoplasms/  83142
6     (brain metast* or brain carcinom* or cerebral metast* or
intracranial metast*).mp.  53160
7     5 or 6     132407
8     ErbB Receptors/  108655
9     (egfr* or epidermal growth factor receptor*).mp. 293788
```

```
10    8 or 9     293788
11    4 and 7 and 10   4976
12    Protein Kinase Inhibitors/ 12809
13    Antineoplastic Agents/     319706
14    (Osimertinib or Tagrisso or AZD9291).mp.    8840
15    12 or 13 or 14   338609
16    11 and 15  1361
17    cranial irradiation/ or radiosurgery/ or radiotherapy,
computer-assisted/ or radiotherapy, high-energy/ or radiotherapy,
image-guided/ or x-ray therapy/  244688
18    radiosurg*.mp.   38741
19    (radioherap* or radiation or irradiation).mp.    1319164
20    17 or 18 or 19   1427685
21    16 and 20  380
22    randomized controlled trial.pt.  0
23    controlled clinical trial.pt.    0
24    randomized.ab.   931758
25    clinical trials as topic.sh.     2
26    randomly.ab.     575626
27    trial.ti.  427801
28    22 or 23 or 24 or 25 or 26 or 27 1619732
29    exp animals/ not humans.sh. 33733423
30    28 not 29  117224
31    21 and 30  0
```

No trials identified.

3 CENTRAL

The same search strategy for Medline (OVID) given above was run in CENTRAL (OVID).

```
EBM Reviews - Cochrane Central Register of Controlled Trials
<February 2024>

1     Carcinoma, Non-Small-Cell Lung/  6570
2     lung cancer.mp.  24741
3     (lung metast* or lung tumo* or lung carcinoma*).mp.    3326
4     1 or 2 or 3      26535
5     cerebral ventricle neoplasms/ or infratentorial neoplasms/ or
supratentorial neoplasms/  215
6     (brain metast* or brain carcinom* or cerebral metast* or
intracranial metast*).mp.  2621
7     5 or 6     2833
8     ErbB Receptors/ 1000
9     (egfr* or epidermal growth factor receptor*).mp. 16518
10    8 or 9     16642
11    4 and 7 and 10   314
12    Protein Kinase Inhibitors/ 1763
13    Antineoplastic Agents/     10474
14    (Osimertinib or Tagrisso or AZD9291).mp.    464
15    12 or 13 or 14   12116
```

```
16    11 and 15  102
17    cranial irradiation/ or radiosurgery/ or radiotherapy,
computer-assisted/ or radiotherapy, high-energy/ or radiotherapy,
image-guided/ or x-ray therapy/  1446
18    radiosurg*.mp.  1276
19    (radioherap* or radiation or irradiation).mp.    39851
20    17 or 18 or 19  40466
21    16 and 20  23
22    randomized controlled trial.pt.  0
23    controlled clinical trial.pt.    0
24    randomized.ab.  715431
25    clinical trials as topic.sh.     40735
26    randomly.ab.    323935
27    trial.ti.  436335
28    22 or 23 or 24 or 25 or 26 or 27 1151312
29    exp animals/ not humans.sh. 3681
30    28 not 29  1148440
31    21 and 30  22
32    Carcinoma, Non-Small-Cell Lung/  6570
33    lung cancer.mp.  24741
34    (lung metast* or lung tumo* or lung carcinoma*).mp.    3326
35    32 or 33 or 34  26535
36    cerebral ventricle neoplasms/ or infratentorial neoplasms/ or
supratentorial neoplasms/  215
37    (brain metast* or brain carcinom* or cerebral metast* or
intracranial metast*).mp.  2621
38    36 or 37   2833
39    ErbB Receptors/  1000
40    (egfr* or epidermal growth factor receptor*).mp. 16518
41    39 or 40   16642
42    35 and 38 and 41 314
43    Protein Kinase Inhibitors/  1763
44    Antineoplastic Agents/     10474
45    (Osimertinib or Tagrisso or AZD9291).mp.    464
46    43 or 44 or 45  12116
47    42 and 46  102
48    cranial irradiation/ or radiosurgery/ or radiotherapy,
computer-assisted/ or radiotherapy, high-energy/ or radiotherapy,
image-guided/ or x-ray therapy/  1446
49    radiosurg*.mp.  1276
50    (radioherap* or radiation or irradiation).mp.    39851
51    48 or 49 or 50  40466
52    47 and 51  23
53    randomized controlled trial.pt.  0
54    controlled clinical trial.pt.    0
55    randomized.ab.  715431
56    clinical trials as topic.sh.     40735
57    randomly.ab.    323935
58    trial.ti.  436335
59    53 or 54 or 55 or 56 or 57 or 58 1151312
60    exp animals/ not humans.sh. 3681
```

```
61    59 not 60  1148440
62    52 and 61  22
```

22 trials.

4 CINAHL

```
S1    carcinoma, non-small-cell lung            20,050
S2    TX lung cancer          101,807
S3    TX (lung cancer or lung neoplasms or lung tumor or lung
adenocarcinoma)         122,985
S4    S1 OR S2 OR S3          124,108
S5    cerebral ventricular system OR infratentorial tumor OR supratentorial
tumor       1,821
S6    TX brain metastases OR TX ( brain cancer or brain tumor or brain
malignant )       40,305
S7    S5 OR S6          41,695
S8    erbB receptors          891
S9    TX (egfr inhibitor or epidermal growth factor receptor inhibitor)
      6,684
S10   S8 OR S9          7,213
S11   S4 AND S7 AND S10       1,069
S12   protein kinase inhibitors           7,872
S13   antineoplastic agents         85,143
S14   TX osimertinib OR TX tagrisso OR TX AZD9291           1,771
S15   S12 OR S13 OR S14       91,387
S16   S11 AND S15       404
S17   cranial irradiation OR radiosurgery OR ( radiotherapy or radiation
treatment or radiation therapy )          95,135
S18   TX radiosurgery         8,775
S19   TX (radiotherapy or radiation therapy or cancer radiotherapy)
      137,181
S20   S17 OR S18 OR S19       141,641
S21   S16 AND S20       226
S22   PT (randomised controlled trial or randomized controlled trial or
rct)        157,133
S23   PT (controlled trial or randomized controlled trial)        157,133
S24   AB randomized           212,152
S25   MW clinical trials as topic   0
S26   MW clinical trial       683
S27   AB randomly       111,832
S28   TI trial          191,988
S29   S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28         443,255
S30   humans or people or individuals or human beings       3,249,607
S31   S29 AND S30       330,456
S32   S21 AND S31       13
```

13 trials.

5 Clinicaltrials.gov

```
Condition:   Carcinoma, Non-Small-Cell Lung
Other terms: Brain metastases
Intervention/treatment: Osimertinib
```

Filter:	Interventional studies

29 trials found.

6 WHO Clinical trials Registry

lung cancer AND brain metast* AND osimertinib

17 trials found.

7 Trials identified

A review of all results gave a total of 2 eligible trials.

OUTRUN: A Randomised Phase II Trial of Osimertinib With or Without SRS for EGFR Mutated NSCLC With Brain Metastases. https://ClinicalTrials.gov/show/NCT03497767.

LUOSICNS: Study of Osimertinib + SRS vs Osimertinib Alone for Brain Metastases in EGFR Positive Patients With NSCLC. https://ClinicalTrials.gov/show/NCT03769103.

STARLET: Supplementary Two

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line/Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 1, p1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 84, p4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 64-68, P3
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	P3
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P7-8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P8

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	NA
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P11-12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P11-12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P12-13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P12-13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P12-13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA as IPD
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA as IPD
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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

Table of Contents

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
Dr Cheryl Ho	Trial Medical Oncology Chair (LUOSICNS)	Cheryl Ho Digitally signed by Cheryl Ho Date: 2024.02.17 12:45:54 -08'00' Cheryl Ho
Prof Ian Marschner	Head of Statistics NHMRC Clinical Trials Centre	Ian Marschner Digitally signed by Ian Marschner Date: 2024.02.29 11:54:04 +11'00' Ian Marschner
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.

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

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

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

References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1.
2. Higgins JPT SJ, Page MJ, Elbers RG, Sterne JAC. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane, 2022; 2022.
3. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
4. Luchi T, Shingyoji M, Sakaida T, Hatano K, Nagano O, Itakura M, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer. 2013;82(2):282-7.
5. Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. The Lancet. 2005;365(9470):1591-5.
6. Aalen O. Nonparametric Estimation of Partial Transition Probabilities in Multiple Decrement Models. The Annals of Statistics. 1978;6(3):534-45, 12.
7. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis [doi:10.1037/1082-989X.3.4.486]. US: American Psychological Association; 1998.

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