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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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