


BMJ Open Protocol for a phase II randomised controlled trial of TKI alone versus TKI and local consolidative radiation therapy in patients with oncogene driver-mutated oligometastatic non-small cell lung cancer

Anil Tibdewal ¹, JaiPrakash Agarwal,¹ Naveen Mummudi,¹ Vanita Noronha,² Kumar Prabhash,² Vijay Patil,² Nilendu Purandare,³ Amit Janu,⁴ Rajiv Kaushal,⁵ Sadhna Kannan⁶

To cite: Tibdewal A, Agarwal J, Mummudi N, *et al.* Protocol for a phase II randomised controlled trial of TKI alone versus TKI and local consolidative radiation therapy in patients with oncogene driver-mutated oligometastatic non-small cell lung cancer. *BMJ Open* 2021;**11**:e041345. doi:10.1136/bmjopen-2020-041345

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-041345>).

Received 09 June 2020

Revised 19 November 2020

Accepted 01 December 2020



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Anil Tibdewal;
aniltibdewal@gmail.com

ABSTRACT

Introduction Tyrosine kinase inhibitors (TKIs) have significantly improved the progression-free survival (PFS) of metastatic non-small cell lung cancer (NSCLC) with oncogene mutations of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) compared with systemic therapy alone. However, the majority eventually develop resistance with a median PFS of 8–12 months. The pattern of failure studies showed disease relapse at the original sites of the disease-harboring resistant tumour cells.

Methods and analysis This study is designed as a phase II randomised controlled trial to evaluate the efficacy of local consolidative radiation therapy (LCRT) in addition to TKI in upfront oligometastatic NSCLC. Patients will be screened at presentation for oligometastases (≤ 5 sites) and will start on TKI after confirmation of EGFR or ALK mutation status. After initial TKI for 2–4 months, eligible patients will be randomised in a 1:1 ratio with stratification of oligometastatic sites (1–3 vs 4–5), performance status of 0–1 versus 2 and brain metastases. The standard arm will continue to receive TKI, and the intervention arm will receive TKI plus LCRT. Stereotactic body radiation therapy will be delivered to all the oligometastatic sites. The primary end point is PFS, and secondary end points are overall survival, local control of oligometastatic sites, toxicity and patient-reported outcomes. The sample size calculation took a median PFS of 10 months in the standard arm. To detect an absolute improvement of 7 months in the interventional arm, with a one-sided alpha of 5% and 80% power, a total of 106 patients will be accrued over a period of 48 months.

Ethics and dissemination The study is approved by the Institutional Ethics Committee II of Tata Memorial Centre, Mumbai, and registered with Clinical Trials Registry—India, CTRI/2019/11/021872, dated 5 November 2019. All eligible participants will be provided with a participant information sheet and will be required to provide written informed consent for participation in the study. The study results will be presented at a national/international

Strengths and limitations of this study

- The study addresses the role of local consolidation radiation therapy in oligometastatic (OM) non-small cell lung cancer (NSCLC) with epidermal growth factor receptor and anaplastic lymphoma kinase mutations.
- The study incorporates randomisation after 2–4 months of initial tyrosine kinase inhibitor therapy, thereby selecting patients who do not have progressive disease.
- The definition of OM as defined in the literature and treatment of primary disease.
- There is no published literature on consolidation radiation therapy in OM driver-mutated NSCLC.
- It is a single-centre study in a developing country.

conference and will be published in a peer-reviewed journal.

INTRODUCTION

Lung cancer is the most common cause of cancer-related mortality worldwide.¹ In India, lung cancer is the second most common cancer and among the top three causes of cancer-related mortality.² Over the last decade, major advances have been made in the treatment of non-small cell lung cancer (NSCLC), which include the use of tyrosine kinase inhibitors (TKIs), immunotherapy and the recognition of oligometastases (OM) as a distinct entity. The clinical use of the first two is supported by well-conducted phase III trials. However, there are no phase III randomised studies evaluating the role of radiation therapy (RT) in the OM setting. While the concept of OM in oncology is not

new, it has gained momentum across tumour types only in the last 5–6 years.^{3,4}

It is well known that using TKIs for patients with metastatic NSCLC with known mutations in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) can produce a dramatic improvement in the progression-free survival (PFS) and overall survival (OS). TKI therapy against EGFR has resulted in a doubling of median PFS up to 10–12 months compared with the 4–5 months with standard platinum-doublet chemotherapy.^{5–11} Nevertheless, the majority of the patients eventually progress within a year, primarily due to the acquired resistance in the EGFR kinase domain.^{12–13} In EGFR-driven NSCLC, the most common acquired resistance is through T790M point mutation in exon 20 of the EGFR gene.^{14–15} Similarly, resistance to ALK-directed TKI develops through a variety of mechanisms, including acquiring ALK mutations; however, the precise mechanisms are not clear.¹⁶ Osimertinib and alectinib, which represent higher generation TKI against EGFR and ALK, respectively, show a superior PFS and OS compared with the older generation drugs.^{17–18} But their use is limited by cost, especially in developing countries where healthcare expenses are mostly borne by the individual rather than the government or private insurance companies.

Treatment options after progression are limited and are guided by the first-line therapy used, the status of T790M mutations, the patient's performance status (PS) and affordability.^{19–20} For patients who develop widespread metastases, treatment with higher generation TKI or systemic chemotherapy is the preferred option.²¹ For the 20%–40% of patients who present with oligoprogression at the site of the primary disease,^{22–23} local therapy using radiation or surgery in addition to the ongoing systemic therapy has shown benefit.^{22–25} The brain appears to be the most common site of first progression because of poor penetration of first-generation TKIs into the central nervous system.²² Unfortunately, 20%–30% of patients who progress are unable to take the further line of therapy because of poor PS, a refusal for chemotherapy or unaffordability for newer TKIs.^{26–27}

The most common pattern of disease failure in patients with metastatic NSCLC is a failure at the primary site, followed by widespread distant metastases. The pattern of disease spread in some patients with NSCLC is unique where they present with only a single or a few sites of metastatic disease referred to as OM.²⁸ Historically, patients presenting with OM to the brain, adrenal glands and liver from different primaries like colorectal cancer, osteosarcoma, breast cancer and others have been offered curative treatment.^{29–31} One of the earliest randomised comparisons with fewer than three brain metastases treated with stereotactic radiosurgery showed good local control (LC) of brain lesions but failed to show any significant OS benefit.²⁹ However, recently reported prospective randomised studies have demonstrated a significant benefit in various survival outcomes, including OS for patients with OM from most cancer sites.^{32–33} Improved

outcome in patients with OM disease has been recognised by the eighth edition of American Joint Committee on Cancer staging of NSCLC, where M1b has been introduced to distinguish patients with a single extrathoracic metastasis from M1c, which represents widespread metastases.³⁴

The most important prognostic factors that have been associated with better outcomes in patients with OM treated with curative intent therapy are favourable biology (like EGFR/ALK mutations), limited volume of disease, treatable or controlled primary, good PS and adequate control with initial systemic therapy.^{35–39} Combining TKI-directed therapy and local ablative therapy to all OM sites has not been studied in a prospective randomised manner. Local consolidation therapy (LCT) with either surgery or RT in the form of stereotactic body radiation therapy (SBRT) or radiofrequency ablation (RFA) to all the OM sites including primary disease demonstrated benefit in LC and survival outcomes.

Mechanism of action of ablative radiotherapy in an OM setting

Advances in radiation planning and treatment techniques have enabled precise delivery of very high doses of radiation to the target while reducing the doses to the adjacent normal tissues. Such high doses can be delivered in a single fraction called stereotactic radiosurgery (SRS) or multiple fractions referred to as SBRT. The ablative radiation doses cause direct damage to the endothelial cells of tumour vasculature in addition to the indirect cell death from DNA damage, leading to superior tumour control than with conventional radiation. In addition, the direct cell-kill and apoptosis lead to the release of tumour-associated antigens and stimulate a local and systemic immune response through various mechanisms. This systemic immune response is thought to be responsible for the abscopal effects of local ablative radiotherapy where the distant non-irradiated site also shows tumour control without receiving any local therapy. Furthermore, this mechanism of immune response helps to enhance the response to immunotherapy and is referred to as the vaccine effect.^{40–41}

The hypothesis for upfront LCT in driver-mutated NSCLC

In the majority of the patients, progression after first-line TKIs usually occurs at the already known sites of gross disease.^{23–42–45} It is believed that resistant tumour cell clones develop at these sites and metastasise further, especially in NSCLC with driver mutations. Hence, it is reasonable to hypothesise that providing LCT along with TKI to all the disease sites in patients with OM NSCLC can potentially delay the progression and improve survival.^{46–47} In addition, ablative doses of radiation to residual disease could evoke a systemic immune response and abscopal effects from altered tumour microenvironment and systemic immune response. This may be especially true for EGFR-mutated NSCLC, which is relatively more sensitive to radiation.⁴⁸ Selecting responders after a few cycles of TKIs helps in identifying patients with

favourable disease biology by excluding those with early disease progression.

Evidence for LCT in NSCLC without oncogene mutation

In OM NSCLC without EGFR or ALK mutation, the addition of LCT after initial standard therapy compared with maintenance treatment alone has significantly improved the PFS and OS in two phase II randomised studies. Gomez *et al* randomly assigned patients with one to three OM sites into LCT with standard maintenance therapy (SMT) versus SMT alone after completion of systemic therapy. After a median follow-up of 38.8 months, they reported that long-term outcomes, both PFS and OS, were in favour of the LCT arm (median PFS, 23.1 vs 14.2, $p=0.017$; median OS, 41.2 vs 17.0 months $p=0.017$).^{39 49} Similarly, Iyengar *et al* randomised 29 patients with one to five OM sites into SMT alone versus stereotactic ablative body radiotherapy (SABR) to all sites of gross disease followed by SMT. They also demonstrated a significant benefit in PFS with SABR 9.7 months versus 3.5 months ($p=0.01$).⁵⁰ Both reported no additional grade 3 or higher toxicities. Palma *et al* also compared SABR in addition to standard of care (SOC) vs SOC alone in one to five metastatic sites from different primary tumours (including 18 patients with NSCLC) and demonstrated improvement in OS.³³ In subgroup analysis limited to lung primary, improvement in OS with SABR was maintained. There are various other studies that have shown that local RT in addition to the standard systemic treatment showed a greater benefit when compared with systemic treatment alone.

Evidence for LCT in NSCLC with oncogene mutation

There are at least two retrospective studies that have evaluated the role of LCT in addition to TKI alone. Hu *et al* evaluated 231 patients with OM lung adenocarcinoma with one to five sites of OM (confined to one organ) who received the first-generation TKI alone or TKI plus LCT with an interval of ≤ 3 months between them. They showed an improvement in PFS from 10 to 15 months ($HR=0.6$, $p=0.000$) and in OS from 21 to 34 months ($HR=0.59$, $p=0.001$).⁴⁶ Multivariate analysis revealed LCT as an independent prognostic factor for PFS and OS. Similarly, Xu *et al* evaluated 145 patients with OM disease with EGFR mutations treated with TKI alone versus those who received LCT in the form of radiotherapy, surgery or both. They also reported a better median PFS (20.6 vs 13.9 months; $p<0.001$) and median OS (40.9 vs 30.8 months; $p=0.001$) in favour of the group that received LCT.⁴⁷ Another small study by Elamin *et al* ($n=12$) also showed improved PFS with LCT when compared with first-line TKI alone ($p=0.002$).⁵¹

Although the role of local consolidative therapy using SBRT for OM NSCLC has been evaluated in phase II randomised studies, they did not specifically evaluate its role in patients with oncogene driver mutation. The patients with driver mutations are distinct in many ways from those without driver mutations and are listed below:

1. Patients with driver mutations have a long and sustained response to TKI alone compared with the non-driver mutated patient's response to systemic chemotherapy, and thus have favourable PFS and OS. Therefore, the addition of LCT may not provide significant benefit with an already effective therapy, while the patients live longer and may experience long-term side effects from the addition of LCT, introducing a true equipoise and the need for such a study.
2. Patients with driver mutations on TKIs have a propensity to initially progress at the known sites of the disease, whereas those without driver mutations experience higher rates of distant failure as their first progression after systemic chemotherapy and are known to have favourable outcomes compared with those without driver mutations using TKI alone.
3. EGFR-mutated tumours are known to be relatively more radiosensitive compared with those without any driver mutations and therefore may benefit from the addition of LCT.

Hence, we initiated this phase II randomised controlled trial (RCT) comparing TKI alone versus TKI plus local consolidative radiation therapy (LCRT) to one to five sites of OM NSCLC with EGFR and ALK mutations (CTRI/2019/11/021872) with the hypothesis that patients receiving local consolidative therapy along with TKI will have superior median PFS compared with those receiving TKI alone.

MATERIAL AND METHODS

This study is designed as a single-institution, open-label, phase II RCT, approved by the institutional ethics committee (Project No. 3338). All patients with NSCLC with positive oncogene mutation (EGFR and ALK) and ≤ 5 sites of OM will be screened for this study. If eligible, patients will be screened for the study at diagnosis; however, they would undergo randomisation only after a minimum of 2 months and a maximum of 4 months of TKI therapy. Only those patients with progressive disease based on clinical and imaging criteria (RECIST (Response Evaluation Criteria In Solid Tumours) version 1.1) would become ineligible for the study.

Eligible patients will be educated about this study in their native language by the investigators and will be given an institutional review board (IRB)-approved informed consent document (online supplemental file 1). For biological samples and radiological image analysis, additional consent will be taken (online supplemental file 1). After written informed consent is provided, patients will be randomised between the standard arm—TKI alone and the interventional arm—TKI plus LCRT (figure 1). Patients will be randomised on a 1:1 basis using stratified block randomisation with a computer-generated random sequence. Randomisation will be done by an independent statistician from the Clinical Research Secretariat Department. This study hypothesises that the addition of

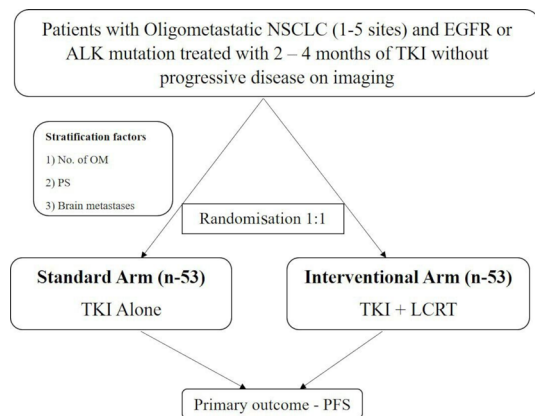


Figure 1 Study schema. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; LCRT, local consolidative radiation therapy; NSCLC, non-small cell lung cancer; OM, oligometastases; PFS, progression-free survival; PS, performance status.

LCRT in the form of SBRT to all sites of OM (≤ 5) will improve the outcomes compared with TKI alone.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The end points of this phase II RCT are as follows.

Primary end points

1. To compare the median PFS between the two study groups where the PFS is defined as the duration between the date of randomisation and the date of progression or death whichever is earlier and patients will be censored at their last follow-up .

Secondary end points

1. To compare the OS between the two study groups where OS is defined as the duration between the date of randomisation and the date of death, irrespective of the cause of death where patients are censored at their last follow-up if alive.
2. To evaluate LC rates of the treated sites with LCRT.
3. To evaluate the differences in the patient-reported outcomes using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core (EORTC QLQ-C30) and its Lung Cancer (LC13) Module questionnaires between the two groups.
4. To compare treatment-related toxicity between the two study groups using National Cancer Institute Common Toxicity Criteria version 5.0.

Radiomics end points

1. To evaluate the textural features of all metastatic and primary disease sites using the TexRAD software (TexRAD, Cambridge UK).
2. To evaluate the differences in the textural features between pretreatment and post-treatment images in both the groups and correlate with various survival outcomes.

Translational end point

To capture and measure the circulating tumour cells (CTCs) in the blood sample at the time of randomisation and 3, 6 and 12 months after treatment completion, and their correlation with the survival outcomes.

Inclusion criteria

1. Age >18 years.
2. Eastern Cooperative Oncology Group (ECOG) PS of 0–2.
3. Pathologically proven diagnosis of NSCLC with oncogene driver mutation (EGFR or ALK).
4. Patients who have received at least 2 months but not more than 4 months of TKI therapy without disease progression.
5. At least one site of distant metastases but not more than five sites of metastatic disease (≤ 3 metastatic lesions in one organ will be eligible) excluding primary tumour and regional nodes.
6. Suitable for LCRT.
7. For women with childbearing potential, negative serum or urine pregnancy test within 14 days of study randomisation.
8. Signed written informed consent form.

Exclusion criteria

1. Progressive disease after an initial 2–4 months of TKI therapy.
2. ≥ 3 metastatic lesions in one organ.
3. Not suitable for LCRT.
4. Not suitable for continuation of TKI therapy due to toxicity at the time of randomisation.
5. Patients with a history of RT to the thorax.
6. Patients with second malignancy (synchronous or metachronous).
7. Severe, active comorbidity defined as follows:
 1. Unstable angina and/or congestive heart failure requiring hospitalisation within the last 6 months.
 2. Transmural myocardial infarction within the last 6 months.
 3. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalisation or precluding study therapy at the time of registration.
8. Pregnancy confirmed using a urine pregnancy test or beta-human Chorionic Gonadotropin (hCG) levels.

Patients would be considered eligible in the following case scenarios provided the patient has ≤ 5 sites of metastases at the time of diagnosis

1. At the time of diagnosis or during the initial TKI therapy, if symptomatic osseous metastasis requires surgical decompression or stabilisation and receives palliative RT, or receives palliative RT alone, such a patient will be eligible for the study, provided the treated site is controlled. The treating radiation oncologist (RO) will decide the dose of the subsequent course of RT for the treated site.

2. At diagnosis or before randomisation, if the patient presented with one to three symptomatic brain metastases and underwent surgical resection or whole-brain RT with boost or SRS, such a patient will be eligible for the study.
3. Patients with a complete radiographic resolution of pleural effusion (PE) after receiving initial TKI therapy on a response assessment CT scan would become eligible for participating in the study.

Prerandomisation assessment

All eligible patients would undergo response evaluation, as per institutional policy, after the initial 2–4 months of TKI therapy, which includes a thorough clinical history and physical examination, PS assessment, contrast-enhanced CT (CECT) of the thorax and abdomen (positron emission tomography (PET)-CECT preferable but not mandatory for study requirements), MRI of the brain with gadolinium contrast if not done at baseline and pulmonary function test. Patients who do not have progressive disease according to RECIST version 1.1⁵² on the response assessment CT scan will remain eligible for this study and will be recruited after obtaining written informed consent. Patients will then be randomly assigned with a 1:1 allocation to either study arms. Patients will be stratified for the number of OM sites (1–3 vs 4–5), PS (0–1 vs 2) and the presence or absence of brain metastases.

Primary and OM site assessment

The regional node for NSCLC includes hilar, mediastinal and supraclavicular nodes as mentioned in the International Association of Study for Lung Cancer staging guidelines.⁵³ The feasibility of primary and nodal disease for LCRT will be decided by the treating RO as per the institutional policy in the same manner as in locally advanced NSCLC. The total number of distant metastases and the number of metastases in organs involved with metastases would be confirmed by the institutional radiologist in a multidisciplinary joint clinic. Biopsy confirmation of the involvement of metastatic site(s) is desired but not mandatory. The involvement of the adjacent vertebrae by direct

extension would be counted as one and not two sites of OM. A final decision regarding the status of the indeterminate parenchymal lung nodule(s) or other metastatic sites, detected on baseline imaging, will be taken based on the response imaging before randomisation in a multidisciplinary joint clinic.

STUDY ARMS

TKI alone (standard arm)

After randomisation, all patients in this arm will continue the same TKI drug as started at the time of initial treatment in both the arms. Standard doses of appropriate TKIs will be given as per the institutional policy and will continue until progression or toxicity precludes its further use. Patients with symptoms from the primary or the metastatic sites will remain eligible to receive palliative RT as per the current institutional standard of care.

TKI plus LCRT (interventional arm)

Patients will receive LCRT to all the OM sites and the primary disease and to the involved regional lymph nodal regions along with the ongoing TKI. All patients will start LCRT within 4 weeks of randomisation. If any of the OM sites have a CR or the lesion is too small in size for RT planning and dose delivery, then that lesion will not be treated with LCRT and will be observed. A separate log of such sites will be kept for further analysis. Immobilisation, contouring and planning will be done as per the institutional guidelines for SBRT. A list of acceptable dose fractionation regimens of LCRT for primary and OM sites is given in [table 1](#). Deviation from these dose guidelines is not preferable until deemed necessary by the RO depending on individual case scenarios.

Primary and nodal disease

Total radiation dose and fractionation for each site would be decided by the treating RO depending on the extent of the primary tumour and organs at risk. The primary tumour without any nodal involvement will be treated with SBRT with doses depending on the location as given

Table 1 Suggested local consolidative radiation therapy doses according to oligometastatic sites

Site	Location	Dose per fraction (Gy)	Number of fractions	Total dose (Gy)	Frequency
Lung	Peripheral	12	5	60	Alternate day
	Central	7.5	8	60	Alternate day
	Ultra-central	5	10	50	Daily
Bone	Spine	8–12 or 24	3–2 or SF	24	Alternate day
	Non-spine	7	5	35	Alternate day
Brain	Single lesion	18–24	1	18–24	Single
	1–3 lesions	18–24 or 5	1 or 10	18–24 or 50	Daily
Adrenal	Any	7 - 10	5	35–50	Alternate day
Liver	Any	7 - 10	5	30–50	Alternate day

SF, Single fraction.

**Table 2** Follow-up visits and procedures

Assessment	Initial before randomisation	First follow-up at 3 months (± 2 weeks)	Thereafter every 3 months (± 2 weeks) till 2 years	After 2 years, 6 months (± 4 weeks) until 5 years
Physical examination	+	+	+	+
Performance status	+	+	+	+
Assessment by RO	+	+	+	+
CECT (T+A+P)	+	+	+	+
Toxicity	+	+	+	–
MRI of brain	+	As indicated	As indicated	As indicated
PET-CT	Not required (preferred)	Not required	As indicated	As indicated
EORTC QLQ C30	+	+	+ (At 6 months and 12 months)	–

CECT (T+A+P), contrast-enhanced CT of thorax, abdomen and pelvis; PET, positron emission tomography; RO, radiation oncologist.

in table 1. Primary along with the nodal disease will be treated with 40–55 Gy in 16–22 fractions—2.5 Gy per fraction delivered one time per day and 5 days in a week.

Data collection and safety monitoring

All the data collected will be uploaded in a restricted access database (REDCap) in a password-protected file. Data will be available to the principal and coprincipal investigators and to the statistician team. The study will be monitored by the Data and Safety Monitoring Committee of the hospital at regular intervals. All toxicities, treatment interruptions, or discontinuation and protocol deviations will be recorded and informed to the IRB as specified by the institutional guidelines. Treating ROs can discontinue or withhold the treatment whenever deemed necessary if the patient has significant toxicities or in life-threatening clinical scenarios. Trial modifications/amendments will be informed to IRB and study sponsors, and will be uploaded in the Clinical Trials Registry—India.

Follow-up evaluations

Patients undergoing LCRT will be reviewed one time per week during RT sessions and at LCRT completion for acute toxicity. Patients will be called for first follow-up assessment at 3 months after completion of LCRT. All patients will be followed up every 3-monthly for the first 2 years and then 6-monthly afterwards until 5 years and thereafter annually (table 2). Adherence to study treatment and follow-up will be ensured by allowing easy access to investigators and study staff members. Any serious toxicity during treatment and at follow-up will be documented, informed to IRB, managed appropriately and will be followed up till resolution. Follow-up imaging with CECT of the disease sites will be done at every follow-up. PET-CT will be requested if there is a clinical suspicion of disease recurrence or in patients where CECT is unable to differentiate between treatment-related changes and recurrence. For patients with brain metastases, response evaluation MRI will be done at 3 months and then only on clinical suspicion for neurological progression. Progression will be assessed at follow-up imaging using RECIST criteria by an experienced radiologist. Quality of life (QOL) questionnaires after baseline will be given at 3, 6 and 12 months.

Treatment after progression

At progression in both arms, patients will be treated as per institutional policy and individual case scenarios. Repeat biopsy of the progressive or new metastatic site, if feasible, will be done for the detection of resistant mutations. Osimertinib will be offered if T790M mutation is detected, and for all other patients, systemic therapy will be offered. Higher generation ALK-directed TKI will be started if affordable; otherwise, systemic therapy would be offered. For patients with oligoprogression, ablative therapy like SBRT, surgery or RFA will be used. After ablative therapy for the oligoprogressive disease site, whether the same TKI will be continued or changed will be decided by the treating medical oncologist.

Statistical analysis

To prove the hypothesis of improved PFS from 10 months in the TKI alone standard arm to 17 months in the LCRT plus TKI arm for this phase II study, we need a sample size of 101 patients to detect this difference with 80.0% power and a one-sided alpha of 5% at a 0.05 significance level (HR of 0.5882). Assuming a 5% attrition rate, the total sample size will be 106–53 in the standard arm and 53 in the interventional arm. The median PFS of 10 months in the standard arm is based on various studies,^{7–9 26} whereas that of the LCRT plus TKI arm of 17 months is based on two retrospective studies of Hu *et al* and Xu *et al*.^{46 47} We intend to accrue 25–30 patients per year; hence in 4 years, we aim to complete the accrual of 106 patients with a minimum follow-up of 18 months. All patients will be followed until death or the end of this study whichever is earlier.

Descriptive statistics will be used to display demographic data, and a χ^2 test would be used to evaluate the balance of various patient and tumour characteristics in both the arms. PFS and OS will be calculated by the Kaplan-Meier method in an intention-to-treat analysis, and comparison between arms will be made using the log-rank test. Univariate analysis will be performed by comparing groups with the log-rank test, and multivariate analysis will be performed using the Cox-proportional hazards model. Treatment-related adverse events' frequency and severity would be reported using descriptive statistics. The

patient-reported outcome of QOL would be analysed according to EORTC guidelines. A p value <0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS V.24.0.

Ethics and dissemination

The study is approved by the Institutional Ethics Committee of Tata Memorial Centre, Mumbai (TMC IRB project number 3338). This study is registered prospectively with Clinical Trials Registry—India, CTRI/2019/11/021872, dated 5 November 2019. All eligible participants will be provided with a participant information sheet and will be required to provide written informed consent for participation in the study. The study results will be presented at a national/international conference and will be published in a peer-reviewed journal.

Radiomics aspect of the study using texture analysis

Heterogeneity is a well-known feature of malignancy and is associated with poor tumour biology just as differentiation in grading tumours in histopathology. Heterogeneity could be present between the different metastatic lesions and primary tumours within the same patient. It has also been reported that heterogeneity represents changes in the tumour macroenvironment and microenvironment. Image analysis can be performed using whole tumour or segments of the tumour, and multiple imaging features can be extracted using different platforms. Texture analysis (TA) evaluates the distribution of grey levels, coarseness and regularity. Recently, image analysis using CT, MRI or PET-CT has been used for differentiating between benign and malignant lesions, prediction of treatment response and prognostication of tumours.^{54–56} In this study, TA will be performed on all the OM sites, including primary disease at baseline and at first follow-up. First-order and second-order statistics of the extracted features and clinical characteristics will be tested for their correlation with clinical end points of PFS, OS and LC. This analysis will be done as a substudy of the main project.

Circulating tumour cells

CTCs are cells that have detached from the primary tumour and shed into the circulation. CTCs may home into distant organs and give rise to metastasis as per the seed and soil theory.⁵⁷ It has been reported that CTC count can be used as a prognostic and predictive biomarker.⁵⁸ Recent studies have validated the importance of CTC count in determining the prognosis and predicting the disease recurrence early even when it is occult on radiology.^{59 60} A higher CTC count at baseline and its persistent presence in blood during follow-up assessment are often associated with poor prognosis in NSCLC.^{59 61} Longitudinal monitoring of CTCs in blood at follow-up assessment could guide us in assessing tumour biology, tumour recurrence and treatment at progression. In this study, blood samples will be collected at baseline and 3, 6 and 12 months.

Quality assurance

All patients in arm 2 will be treated after a strict and robust quality assurance protocol adopted at the host institute. The

following requirements will be ensured before the treatment of the individual metastatic site or primary disease:

- Peer review of contouring of each treatment site between the ROs AT, JPA and NM.
- Peer review of treatment plans for target coverage and organs at risk doses by another RO and physicist.
- All the verification images of cone-beam CT will be verified online as well as offline during the radiotherapy treatment audit.

Confidentiality

Study participants' names and personal information will be held in strict confidence and will not be shared publicly. Participant details in case record forms, safety reports and correspondence to IRB will be done with the study identification number and participants' initials. Study investigators will maintain a master list with participants' identification details.

Data sharing statement

Deidentified participant data from this study will not be shared publicly; however, the full protocol will be published along with the primary analysis of the outcomes.

DISCUSSION

TKIs have resulted in a marked improvement in PFS and OS. Even then, nearly half of them relapse at the already known sites of disease and approximately 20%–30% become ineligible for second-line systemic therapy due to several reasons. In selected patients with OM (≤ 5 sites), SBRT was offered to the OM sites in two phase II RCTs which showed a benefit in PFS and OS in favour of LCT after the initial systemic therapy. In the study by Gomez *et al*, 8 of 49 patients had positive oncogene mutation and were associated with an improvement in PFS ($p=0.012$). In contrast, the study by Iyengar *et al* had excluded patients with EGFR or ALK driver mutations.

Currently, there is one phase II RCT by Gomez *et al* that is recruiting patients with OM with sensitising EGFR mutations and is expected to complete by January 2022. They are using osimertinib as TKI either upfront or after progression with first-generation or second-generation TKI. Their primary end point is PFS. Another one is phase III RCT from China, recruiting patients for first-line TKI with or without SBRT in ≤ 5 OM sites with EGFR mutations. The primary end point is PFS. In this study, we will be taking only synchronous OM NSCLC with oncogene mutations treated with different TKIs. Osimertinib is costly for the majority of our patients.

We faced certain challenges while designing the study protocol in our settings. First, the number of sites to be considered as the OM disease was not clear in the literature. We took ≤ 5 sites as the OM state, else the numbers required for the protocol would have been difficult to achieve. In addition, a consensus report defined the OM state as ≤ 5 sites, and ≤ 3 lesions per organ further support our decision.⁶² Second, PE is a common feature in metastatic NSCLC, especially in patients with oncogene mutations.^{63 64} RECIST guidelines classify PE as a non-measurable disease.⁵² There is no clear guideline to suggest whether PE should be classified as an

OM site or not. For this study, we have considered PE as a separate entity, and only those patients where the effusion completely resolves would be considered eligible. Third, the majority of patients who present with symptomatic primary disease, bone or brain metastases are treated with palliative (non-ablative doses) radiation even before the results of oncogene mutation status are available. In such patients, it may become difficult later to account for the doses received initially while planning the LCT. Fourth is the inherent challenges associated with the detection of OM using CECT scan as PET-CT is currently not the standard staging investigation for metastatic NSCLC.

A single-centre study has its own advantages and disadvantages. The advantages are reduced cost of conducting the study, ease of conducting it, better control over the quality assurance of the radiotherapy process and the uniformity of patient management decisions. The disadvantages of a single-centre study are difficulty in timely recruitment of the patients and generalisation of the study results as compared with the multicentric study design. Nevertheless, given the large number of new patients registered with metastatic NSCLC at our institution, we are hopeful of finishing accrual as planned (25–30 patients per year: 4 years for completing recruitment). The study has sought funding from various governmental organisations as well as philanthropic entities and is currently under process.

Author affiliations

¹Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

²Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

³Nuclear Medicine, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁴Radiodiagnosis, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁵Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁶Clinical Research Secreariat, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

Twitter Anil Tibdewal @ANILTIBDEWAL and Vanita Noronha @VanitaNoronha

Acknowledgements We acknowledge the support of Dr Rima Pathak for critical inputs in manuscript preparation.

Contributors AT, KP and JA helped with the concept and design of the study. AT and JA prepared the initial draft of the protocol. AT, JA, KP, NM, VN, SK, VP, NP, AJ, RK and SK prepared the final draft of the protocol. All authors read and approved the final protocol.

Funding This study is reviewed and approved by the Institutional Ethics Committee and will be sponsored partly by the Tata Memorial Hospital. However, the funding is delayed due to the ongoing COVID-19 pandemic. Funding bodies will not have any role in study design modifications, data collection and analysis of the study.

Competing interests VN has received institutional research funding from Amgen, Sanofi India, Dr. Reddy's Laboratories, Intas Pharmaceuticals and Astra Zeneca Pharma India. All research grants have been paid to the institution. KP has received research funding from Dr. Reddy's Laboratories, Fresenius Kabi India, Alkem Laboratories, Natco Pharma, BDR Pharmaceuticals and Roche Holding AG (all research grants paid to the institution and are unrelated to this study project).

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Anil Tibdewal <http://orcid.org/0000-0002-0374-0800>

REFERENCES

- World Health Organization. Globocan 2018 : All Cancers. *Int Agency Res Cancer* 2019;1:1–2.
- Globocan. *International agency for research on cancer.India Factsheet*, 2018.
- Hellman S, Weichselbaum RR. Oligometastases. *JCO* 1995;13:8–10.
- Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011;8:378–82.
- Wu Y-L, Lu S, Lu Y, *et al*. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib Versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2018;13:1539–48.
- Wu Y-L, Cheng Y, Zhou X, *et al*. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (Archer 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:1454–66.
- Maemondo M, Inoue A, Kobayashi K, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–8.
- Rosell R, Carcereny E, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
- Mitsudomi T, Morita S, Yatabe Y, *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–8.
- Zhou C, Wu Y-L, Chen G, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (optimal, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–42.
- Shaw AT, Kim D-W, Nakagawa K, *et al*. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368:2385–94.
- Pao W, Miller VA, Politi KA, *et al*. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005;2:e73–35.
- Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. *Eur Respir Rev* 2014;23:356–66.
- Sequist LV, Waltman BA, Dias-Santagata D, *et al*. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
- 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.
- Katayama R, Shaw AT, Khan TM, *et al*. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med* 2012;4:120ra17–120.
- 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.
- Hida T, Nokihara H, Kondo M, *et al*. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390:29–39.
- Patil VM, Noronha V, Joshi A, *et al*. Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open* 2017;2:e000168.

- 20 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.
- 21 Under the aegis of Lung Cancer Consortium Asia (LCCA), Indian Cooperative Oncology Network (ICON), Indian Society of Medical & Pediatric Oncology (ISMPO), *et al.* Indian consensus statement for treatment of advanced non small cell lung cancer: first line, maintenance, and second line. *Indian J Cancer* 2017;54:89–103.
- 22 Xu Q, Liu H, Meng S, *et al.* First-Line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease. *J Cancer* 2019;10:522–9.
- 23 Rusthoven KE, Hammerman SF, Kavanagh BD, *et al.* Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. *Acta Oncol* 2009;48:578–83.
- 24 Weickhardt AJ, Scheier B, Burke JM, *et al.* Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1807–14.
- 25 Basler L, Kroeze SGC, Guckenberger M. SBRT for oligoprogressive oncogene addicted NSCLC. *Lung Cancer* 2017;106:50–7.
- 26 Patil VM, Noronha V, Joshi A, *et al.* Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open* 2017;2:e000168:10–18.
- 27 Noronha V, Patil VM, Joshi A. Ge FI tinib versus Ge FI tinib plus pemetrexed and carboplatin chemotherapy in EGFR. *Mutated Lung Cancer* 2020:1–14.
- 28 Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8–10.
- 29 Andrews DW, Scott CB, Sperduto PW. 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 2004;363:1665–72.
- 30 Patchell RA, Tibbs PA, Walsh JW, *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
- 31 Shady W, Petre EN, Gonen M, *et al.* Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes--A 10-year Experience at a Single Center. *Radiology* 2016;278:601–11.
- 32 Sutera P, Clump DA, Kalash R, *et al.* Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys* 2019;103:116–22.
- 33 Palma DA, Olson R, Harrow S, *et al.* Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–8.
- 34 Eberhardt WEE, Mitchell A, Crowley J, *et al.* The IASLC lung cancer staging project. *J Thorac Oncol* 2015;10:1515–22.
- 35 Van den Begin R, Engels B, Collen C, *et al.* The METABANK score: a clinical tool to predict survival after stereotactic radiotherapy for oligometastatic disease. *Radiation Oncol* 2019;133:113–9.
- 36 Li S, Zhu R, Li D, *et al.* Prognostic factors of oligometastatic non-small cell lung cancer: a meta-analysis. *J Thorac Dis* 2018;10:3701–13.
- 37 Ashworth AB, Senan S, Palma DA, *et al.* An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;15:346–55.
- 38 Griffioen GHMJ, Toguri D, Dahele M, *et al.* Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* 2013;82:95–102.
- 39 Gomez DR, Blumenschein GR, Lee JJ, *et al.* Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672–82.
- 40 Shaverdian N, Lisberg AE, Bornazyan K, *et al.* Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 2017;18:895–903.
- 41 Theelen WSME, Peulen HMU, Lalezari F, *et al.* Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol* 2019;5:1276–82.
- 42 Al-Halabi H, Sayegh K, Digamurthy SR, *et al.* Pattern of failure analysis in metastatic EGFR-mutant lung cancer treated with tyrosine kinase inhibitors to identify candidates for consolidative stereotactic body radiation therapy. *J Thorac Oncol* 2015;10:1601–7.
- 43 Patel SH, Rimner A, Foster A, *et al.* Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. *Lung Cancer* 2017;108:109–14.
- 44 Yang J-J, Chen H-J, Yan H-H, *et al.* Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. *Lung Cancer* 2013;79:33–9.
- 45 Park K, Yu C-J, Kim S-W, *et al.* First-Line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor Mutation-Positive Non-Small-Cell lung cancer. *JAMA Oncol* 2016;2:305–12.
- 46 Hu F, Xu J, Zhang B, *et al.* Efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring epidermal growth factor receptor mutations. *Clin Lung Cancer* 2019;20:e81–90.
- 47 Xu Q, Zhou F, Liu H, *et al.* Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. *J Thorac Oncol* 2018;13:1383–92.
- 48 Mak RH, Doran E, Muzikansky A, *et al.* Outcomes After Combined Modality Therapy for EGFR -Mutant and Wild-Type Locally Advanced NSCLC. *Oncologist* 2011;16:886–95.
- 49 Gomez DR, Tang C, Zhang J, *et al.* Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* 2019;37:1558–65.
- 50 Iyengar P, Wardak Z, Gerber DE. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018;4:1–4.
- 51 Elamin YY, Gomez DR, Antonoff MB, *et al.* Local consolidation therapy (lct) after first line tyrosine kinase inhibitor (TKI) for patients with EGFR mutant metastatic non-small-cell lung cancer (NSCLC). *Clin Lung Cancer* 2019;20:43–7.
- 52 Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- 53 Rusch VW, Asamura H, Watanabe H, *et al.* The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–77.
- 54 Chaddad A, Desrosiers C, Toews M, *et al.* Predicting survival time of lung cancer patients using radiomic analysis. *Oncotarget* 2017;8:104393–407.
- 55 Andersen MB, Harders SW, Ganeshan B, *et al.* CT texture analysis can help differentiate between malignant and benign lymph nodes in the mediastinum in patients suspected for lung cancer. *Acta Radiol* 2016;57:669–76.
- 56 Dou TH, Coroller TP, van Griethuysen JJM, *et al.* Peritumoral radiomics features predict distant metastasis in locally advanced NSCLC. *PLoS One* 2018;13:e0206108:1–15.
- 57 Galanzha EI, Shashkov EV, Kelly T, *et al.* In vivo magnetic enrichment and multiplex photoacoustic detection of circulating tumour cells. *Nat Nanotechnol* 2009;4:855–60.
- 58 Punnoose EA, Atwal S, Liu W, *et al.* Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. *Clin Cancer Res* 2012;18:2391–401.
- 59 Lindsay CR, Faugeroux V, Michiels S, *et al.* A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. *Ann Oncol* 2017;28:1523–31.
- 60 Tamminga M, de Wit S, Schuurin E, *et al.* Circulating tumor cells in lung cancer are prognostic and predictive for worse tumor response in both targeted- and chemotherapy. *Transl Lung Cancer Res* 2019;8:854–61.
- 61 Paillet E, Oulhen M, Borget I, *et al.* Circulating Tumor Cells with Aberrant ALK Copy Number Predict Progression-Free Survival during Crizotinib Treatment in ALK-Rearranged Non-Small Cell Lung Cancer Patients. *Cancer Res* 2017;77:2222–30.
- 62 Dingemans A-MC, Hendriks LEL, Berghmans T, *et al.* Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. *J Thorac Oncol* 2019;14:2109–19.
- 63 Froudarakis ME. Pleural effusion in lung cancer: more questions than answers. *Respiration* 2012;83:367–76.
- 64 Saito H, Fukuhara T, Furuya N, *et al.* Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019;20:625–35.