



## **ALKternate**

**A single arm multi-centre translational proof of concept study in *ALK*-rearranged non-small cell lung cancer of alternating lorlatinib with crizotinib after disease progression after prior 2<sup>nd</sup> generation tyrosine kinase inhibitor therapy**

### **Protocol version 5.0**

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# 1 PROTOCOL SYNOPSIS

## Background

Treatment with targeted ALK-inhibitor (ALKi) therapy has revolutionised the management of advanced Anaplastic Lymphoma Kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC). First generation inhibitor crizotinib, then second generation ceritinib and now alectinib have surpassed the prior investigated ALKi's as the gold standard of care as first line therapy for patients with advanced *ALK* gene rearranged NSCLC based on far superior survival.

Regardless, resistance to treatment remains inevitable as most patients will receive multiple lines of ALKi therapy before they eventually die from the disease. Mechanisms of *ALK* dominant resistance are being increasingly recognized, including the development of secondary kinase domain (KD) mutations and copy number gain in the *ALK* gene; or activation of bypass tracts. In a proportion of patients, the cause for drug resistance remains unknown.

Lorlatinib is a 3<sup>rd</sup> generation ALKi active against a broad range of *ALK* gene resistance mutations and has demonstrated superior potency to acquired *ALK* mutations, compared to 1<sup>st</sup> and 2<sup>nd</sup> generation agents. A recent case report demonstrated re-sensitisation to crizotinib by the lorlatinib *ALK* resistance mutation L1198F. Further understanding of patterns and mechanisms of resistance is the key to overcoming and preventing its emergence.

## Hypothesis

Based on the knowledge of the differential patterns of resistance to different ALKis, ALKternate is based on the hypothesis that ALKi-resistance mechanisms are either present at baseline or acquired through selection pressure from ALKi therapy and confer variable resistance to ALKis.

Furthermore, we hypothesise that treating *ALK* NSCLC patients with alternating ALKi's will suppress further clonal selection and drug resistance, leading to longer disease control and increased survival for these patients who have progressed on standard therapy and have no or limited options.

## Aims

To identify whether a fixed alternating schedule of lorlatinib followed by crizotinib followed by lorlatinib and so on is:

- Safe, with a comparable toxicity profile to a continual dosing strategy
- Feasible and active, resulting in prolonged systemic and intracranial disease control via delaying the emergence of secondary ALKi resistance

To determine whether a fixed alternating schedule of lorlatinib followed by crizotinib followed by lorlatinib and so on, will result in suppression of: *ALK* gene resistance KD mutations measurable in circulating tumour (ct) DNA; plasma proteomic drivers; or alternative oncogenic drivers and to explore post hoc whether this approach can be used to identify the development of resistance before progression is evident.

**Primary objective (endpoint)** To determine the time to treatment failure with alternating ALKi therapy (TTTF)\* defined as the time from treatment initiation to treatment discontinuation (months) all cause and compare this to historical reports of continuous therapy (1). Only those who enter alternating therapy will be included in the primary outcome analysis.

\*TTTF defined in Section 4.6 p19

**Secondary objectives (endpoints)**

- TTTF for the whole cohort enrolled on trial (including those with progression on during induction phase i.e. primary lorlatinib resistance)
- Best objective response at any time of the study
- Progression free survival PFS1 and PFS2 (if applicable)
- To determine the overall DCR (CR, PR, SD; systemic and CNS) % after 12 weeks lorlatinib induction and the first cycle of alternating therapy and median
- Overall survival (OS)
- Safety/Toxicity assessment
- PROs/QOL measure analysis
- ctDNA and protein profiling for emergence of ALK kinase domain (KD) mutations and alterations in protein expression

**Design and Interventions**

This is a multi-centre, open label, single arm, proof of concept study with a translational focus using blood to examine genomic and proteomic secondary resistance mechanisms to alternating ALKi therapy; lorlatinib 100mg OD for 12 weeks as induction (cycle 1), then crizotinib 250 mg BID for 4 weeks alternating with lorlatinib 100 mg daily for 8 weeks (cycle 2) and so on, until disease progression (Figure 1.p8)



A 48 hour drug free interval in between alternating drug therapy will occur based on pharmacokinetic drug-drug interaction considerations.

## Population

- Patients with prior confirmed stage IV ALK gene rearranged NSCLC
- Confirmed radiological disease progression on prior therapy
- The most recent line of ALKi being a second generation inhibitor
- Patients who have only had one line of prior therapy if it was a second generation ALKi **are** eligible, as are those whose most recent line of treatment has been a non ALKi provided they fulfill the above
- ECOG performance status  $\leq 1$
- Patients with asymptomatic CNS disease including leptomeningeal are eligible
- Patients with clinically significant CNS progression including leptomeningeal are eligible **only** following surgery or radiotherapy with clinical stability for two weeks and/or stable steroid requirement for at least two weeks

Enrolled patients **MUST** demonstrate systemic **and** central nervous system (CNS) disease control after induction lorlatinib to continue on to the **alternating** therapy sequence of the trial.

## Assessments

**Imaging:** Baseline CT- Chest, Abdomen and Pelvis (CAP) and MRI- Brain (B) then;  
Repeat after induction lorlatinib at week 12 (cycle 1);  
After cycle 2a (crizotinib) at week 16;  
Cycle 2b (lorlatinib) at week 24;  
Cycle 3a (crizotinib) week 28,  
and 3b (lorlatinib) week 36 **then**;  
12 weekly thereafter (cycle 4 on). Reported via RECIST v 1.1

**Safety and Toxicity:** Safety and toxicity will be reviewed based on CTCAE version 4.03 every clinic visit from baseline and every 4 weeks thereafter with an additional review at Cycle 1 Day 15. PROs (FACT-L survey and Beck's Depression Inventory) will be performed at baseline and at clinic visits every 8 weeks until Cycle 3b-4a, then every 12 weekly thereafter. A cognitive assessment (MiniCog) will be performed at baseline, C1-2a, C2a-2b and C3a-3b and where individually clinically indicated.

Clinical history, examination and routine bloods will be reviewed every clinic visit from baseline, Cycle 1 Day 15, Week 4, then 4 weekly thereafter. An ECG will be performed at each visit with drug switch in Cycles 2 and 3, then every 12 weeks thereafter.

**Pharmacokinetic (PK) analysis:** Blood draw between cycle 1-2a and cycle 2a-2b at drug switch. Drug will be stopped 48 hours prior to the start of a new cycle and drug switch.

**Plasma Resistance Profiling:** Patient plasma will be collected and safely stored for *post hoc* ctDNA analysis and identification of circulating genomic and proteomic resistance mechanisms at **baseline; week 12** then **at each change in study drug visit** until cycle 3b, and then 12 weekly thereafter or at each disease progression point if occurring earlier, with a final collection at end of study. A mandated tissue biopsy will be performed at trial entry and at disease progression if deemed clinically safe and feasible.

### Statistical considerations

This is an exploratory pilot study. A minimum sample size of **20 participants** has been arbitrarily chosen to be enrolled in the alternating drug schedule, approximately 10 with CNS disease, from 2 collaborative centres: Royal North Shore Hospital, Sydney (N Pavlakis, M Itchins) and Peter MacCallum Cancer Centre (B Solomon).

The time point of patient eligibility for inclusion in the alternating drug schedule will occur after the 12 week induction lorlatinib phase- thus a small number of patients may potentially drop off if clinically progressing after the lorlatinib induction period. The trial will therefore enrol an estimated **25 participants** allowing for this. Feasibility will be based on the successful demonstration that in patients' entering the alternating phase disease can be controlled after completion of at least one 12 weekly sequence of alternating crizotinib/lorlatinib in at least 10 patients (6 months on therapy). Safety will also be assessed based on patient tolerability of treatment and toxicity data collected.

Historical phase (P) II lorlatinib data will be used to benchmark the survival endpoints which have reported a PFS of 5.5-6.9 months in this patient population treated with continual lorlatinib after prior ALKi (2).

## Study Schema

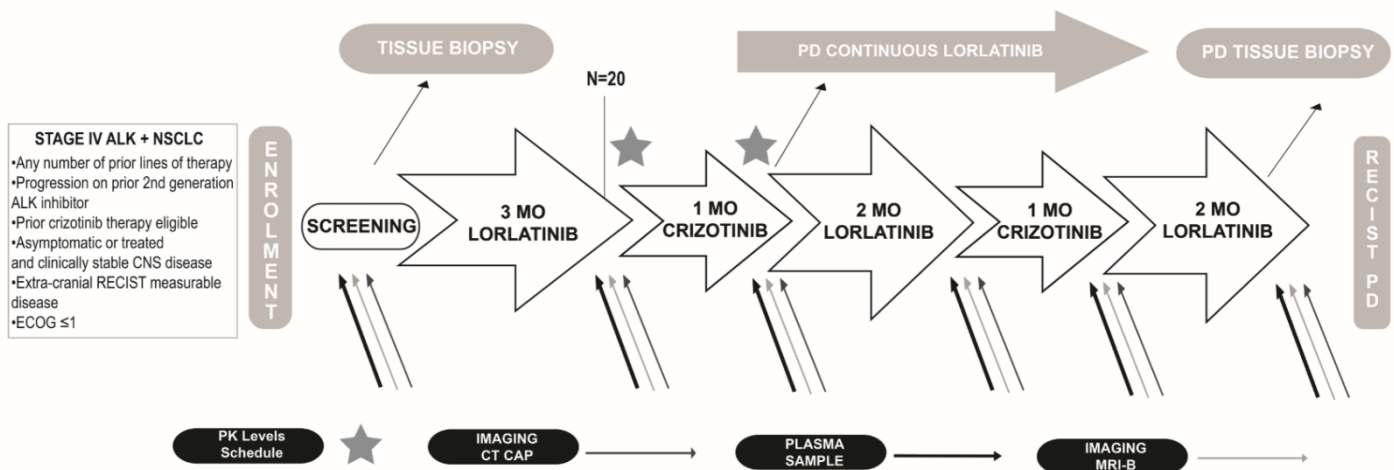


Figure 1. ALKternate study schema including inclusion criteria, trial design and schedule of events

\*The tissue biopsy is **mandated** for the patient and performed at the discretion of the investigator based on safety and feasibility, preferably on a new or progressing lesion. An inability to obtain a tissue biopsy does not exclude patients from enrolling into the trial.

## 2 BACKGROUND

### 2.1 Anaplastic Lymphoma Kinase (ALK) Rearranged NSCLC

ALK rearrangements are found in approximately 3-7% of cases of NSCLC. First reported on by Soda and colleagues in 2007, ALK rearrangements represent a distinct clinical and pathologic subtype of lung cancer with features such as younger age affecting males and females, light or never smoking history and adenocarcinoma histology (3-6).

It has become well recognized that CNS tropism and disease progression in the brain is a frequent complication in patients with ALK-positive (ALK+) NSCLC requiring vigilant monitoring and evaluation via baseline and sequential brain MRI. The CNS is proposed to be a sanctuary site for patients with ALK-rearranged NSCLC, with approximately 25% presenting with CNS disease, and up to 75% eventually progressing in the CNS (2, 7). The diagnosis of uncontrolled CNS metastases has a significant impact on patient wellbeing, causing symptoms, functional impairment, loss of independence and is a significant cause of morbidity in these young patients.

### 2.2 Crizotinib, First Generation ALK-inhibitor

Crizotinib (PF-02341066, Pfizer Oncology, Groton, CT, USA) is a selective ATP-competitive small-molecule inhibitor of ALK and c-Met/Hepatocyte Growth Factor Receptor (HGFR) tyrosine kinases and their oncogenic variants (e.g. ALK fusion proteins or c-Met/HGFR mutant variants). Consistent with these mechanisms of action, crizotinib dose-dependently inhibits phosphorylation and kinase target dependent functions of ALK, c-Met/HGFR, and selected variants in tumour cells both *in vitro* and *in vivo* (8, 9).

### 2.3 Lorlatinib, Third Generation ALK-inhibitor

Lorlatinib (PF-06463922, Pfizer Oncology, Groton, CT, USA) is a novel, oral, reversible, ATP-competitive macrocyclic tyrosine kinase inhibitor (TKI) that targets ALK and ROS1. This potent and highly selective third-generation inhibitor was designed to penetrate the blood–brain barrier and to overcome known *ALK* resistance mutations. In cell-line models, lorlatinib has low nanomolar potency against wildtype ALK and retains potency against ALK-resistant mutants, including *ALK* Gly1202Arg (10). Clinical data have supported lorlatinib's superior efficacy in patients with pan resistant KD mutations and confirmed it is highly brain penetrant (1, 2).

### 2.4 Landscape of Treatment of *ALK* Rearranged Advanced NSCLC

The discovery that patients with *ALK*+ NSCLC were sensitive to the oral tyrosine kinase inhibitor crizotinib (1<sup>st</sup> generation ALKi) led to a wave of new drug discoveries and a series of Phase (P) III randomised controlled trials (RCTs) that established high level evidence for the treatment of these patients. Crizotinib, and then ceritinib (2<sup>nd</sup> generation ALKi) demonstrated superiority over chemotherapy as both first and second line treatments. More recently, alectinib (2<sup>nd</sup> generation ALKi) demonstrated compelling superiority to crizotinib as a first line treatment (7, 11-13). Additionally, both alectinib and ceritinib have much higher CNS penetration and activity than crizotinib (14, 15)\*.

Therefore, identification of an *ALK* rearrangement is key in the management of *ALK*+ lung cancer as it confers sensitivity to treatment with ALK tyrosine kinase inhibitors (TKIs; ALKi). These inhibitors have made major advances over the last decade, with superior PFS and objective response rates (ORR) over conventional chemotherapy in *ALK*+ patients. At present in Australia, the 1<sup>st</sup> generation ALKi crizotinib was until 2018 the standard of care first line, with 2<sup>nd</sup> generation inhibitor ceritinib also reimbursed, without specification for line of therapy (7, 16). Highly positive PIII data have supported alectinib as the new standard of care first line given its superior PFS; control of CNS disease, including delay in CNS metastases and improved toxicity profile compared with crizotinib in the ALEX trials (13, 17). Alectinib became the new first line standard in Japan and in late 2017 is now recommended for first line use by the EMA and US FDA. It was also reimbursed in Australia from Jan 1, 2018. Thus, crizotinib has a diminishing place in the future treatment paradigm of *ALK* rearranged NSCLC.

Compelling early PIII data for second generation ALKi brigatinib and phase I/II for third generation ALKi lorlatinib in treatment naïve and refractory disease have incited interest for their respective front-line PIII clinical trial data (2, 18, 19) However, with alectinib now the standard reimbursed first line therapy in Europe, US and Australia, these agents will need to demonstrate some therapeutic advantage over alectinib to subsequently compete with its position. Without head to head comparative trials, this will require indirect comparisons of efficacy and tolerability in trials compared with crizotinib. With its demonstrated activity in the refractory setting, it is likely that lorlatinib may become the drug of choice in the later line setting and not earlier, unless a clear advantage can be demonstrated.

### 2.5 Acquired Resistance to ALK Tyrosine Kinase Inhibitors

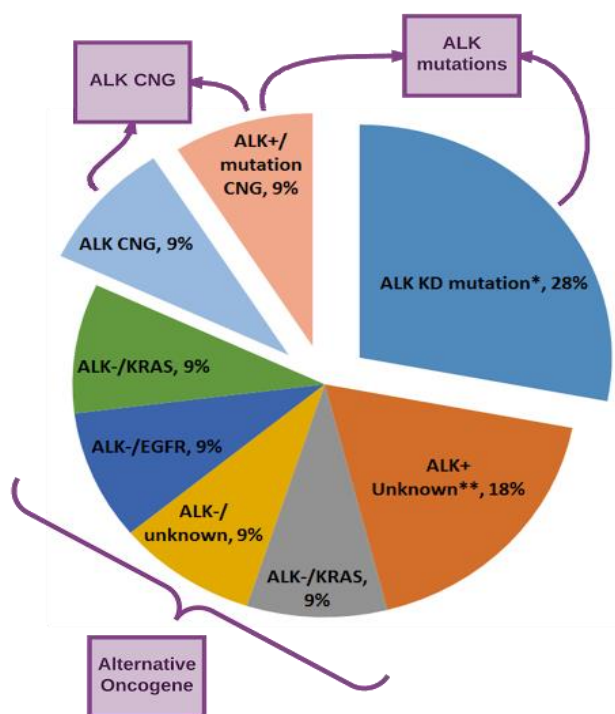
Unfortunately, despite high initial ORR across ALKi therapy, drug resistance is inevitable. An understanding of mechanisms of resistance is rapidly evolving however not completely

explained. Crizotinib has been the most studied as the first ALKi to be developed and available in the clinic. Resistance has been described broadly under *ALK*-dependent and *ALK*-independent pathways (20). In approximately one quarter to one third of cases the mechanism of resistance remains unknown (21).

In *ALK*-dependent drug resistance different *ALK* fusion genes may have differing sensitivities to crizotinib with *EML4-ALK* variant 1 reported to have greater sensitivity than other variants (22); the inverse has been found with lorlatinib (23). Beyond this, the development of *ALK* kinase KD mutations can block or lessen the binding affinity of crizotinib as well as next generation TKIs and increase protein kinase activity (20, 21, 24). The frequency of these mutations increases, and profile differs with the use of second generation ALKis upfront and after each line of therapy. Sensitivity with different ALKis varies with each described KD mutation (2, 25). *ALK* gene amplification may also result in resistance.

A cause of *ALK*-independent resistance may be bypass signalling which can occur with the activation of, and constitutive signalling through, other pathways. Activation of the *EGFR* pathway in this context usually occurs through increased phosphorylation and upregulation of ligands. Rarely, concomitant activating *EGFR* and *KRAS* mutations have also been described, possibly reflecting the emergence of pre-existing clones under selection pressure from crizotinib (26). Transformation to small cell lung cancer has also been demonstrated in case reports (27).

Pharmacologic mechanisms such as inadequate penetration into the CNS may also produce relative therapeutic resistance leading to CNS progression, a problem with crizotinib (28), compared with next generation inhibitors which have superior brain penetrability (2, 18, 29).



**Figure 2 (Left).** *ALK* resistance mechanisms (30) CNG: copy number gain.

**A critical component of the ALKternate Trial will be to monitor patients for the development of ALKi resistance mechanisms, both known and unknown.**

Tissue biopsy will be obtained where feasible, and blood plasma (liquid biopsies) will be utilised. These have the added appeal of overcoming the confounding factor of spatial (and temporal) tumour heterogeneity within tissue occurring through clonal evolution and selection pressure with ALKi therapy (31).

**Table 1 (Below).** *ALK Kinase Domain mutations identified in ALK+ NSCLC and resistance (denoted as +) to different ALKIs [Table adapted from (32)].* Crizotinib and lorlatinib have essentially mutually exclusive resistance profiles, so that tumours resistant to crizotinib due to a KD mutation remain sensitive to lorlatinib. Compound heterozygosity has been reported to re-sensitise to crizotinib, e.g. L1198F plus C1156Y versus C1156Y alone, D1203N plus E1210K versus D1203N alone (highlighted mutations).

<b>ALK Kinase Domain Mutation</b>	<b>Crizotinib</b>	<b>Ceritinib</b>	<b>Alectinib</b>	<b>Brigatinib</b>	<b>Lorlatinib</b>
L1152P/R; F1174C/S/L	+	+			
I1171T/N/S; V1180L	+		+		
S1206C/Y; C1156Y	+				
D1203N; G1269A/S; L1196M; L1198P	+				
L1198F					+
L1198F plus C1156Y					+
E1210K plus D1203N				+	
E1210K plus S1206C				+	
G1202R	+	+	+	+	

## 2.6 Utilising Plasma ‘Liquid Biopsy’ to Investigate Resistance

Known mechanisms of resistance such as mutations, rearrangements and amplification of ALK and other oncogenes will be assessed by next generation sequencing (NGS) of ctDNA (DNA and RNA) using a commercially validated genomic assay. ctDNA analysis has successfully detected ALK KD mutations, e.g. the PII lorlatinib study recently reported the presence of ALK KD mutations in plasma in 24% of ALK+ pre-treated patients (31, 33). This was higher in a retrospective series, with a KD identifiable in 50% (34). The emergence of KD mutations on 3<sup>rd</sup> generation ALKi lorlatinib and any temporal evolution of ctDNA in plasma in patients on ALKi has not been prior reported on.

In addition to NGS to detect changes in genes known to be involved in resistance, proteomic analysis will also be performed on patient plasma. Recent revolutionary advances in mass spectrometry (MS), principally the development of high-resolution data-independent acquisition (DIA) MS methods, have now made it possible to conduct high-resolution proteome mapping in complex biological samples without extensive sample processing (35). One such DIA method, known as Sequential Windowed data independent Acquisition of the Total High-resolution Mass Spectra (SWATH-MS), is now becoming known as the premier method for obtaining comprehensive, consistent and quantitatively accurate proteomics data across many biological samples, including plasma (36, 37).

## 2.7 Rationale for This Study

In Australasia today, most new ALK+ NSCLC patients will commence alectinib as initial therapy and patients having previously received crizotinib will then receive ceritinib or alectinib at progression. Therefore, newly diagnosed patients would be expected to receive

up to two of the currently available ALKis. Even so, long term follow-up data has shown that *ALK+* NSCLC patients receiving multiple therapies have a four-year overall survival (OS) of only 56.6% (38). In a real world cohort of 35 patients treated at Royal North Shore Hospital, 5-yr OS was <30% (39)\*. Despite the availability of three TKIs to treat *ALK+* NSCLC in Australia (crizotinib, ceritinib and alectinib), the inevitability of drug resistance leading to death demonstrates there is an unmet need for new therapies and methods to overcome or delay drug resistance.

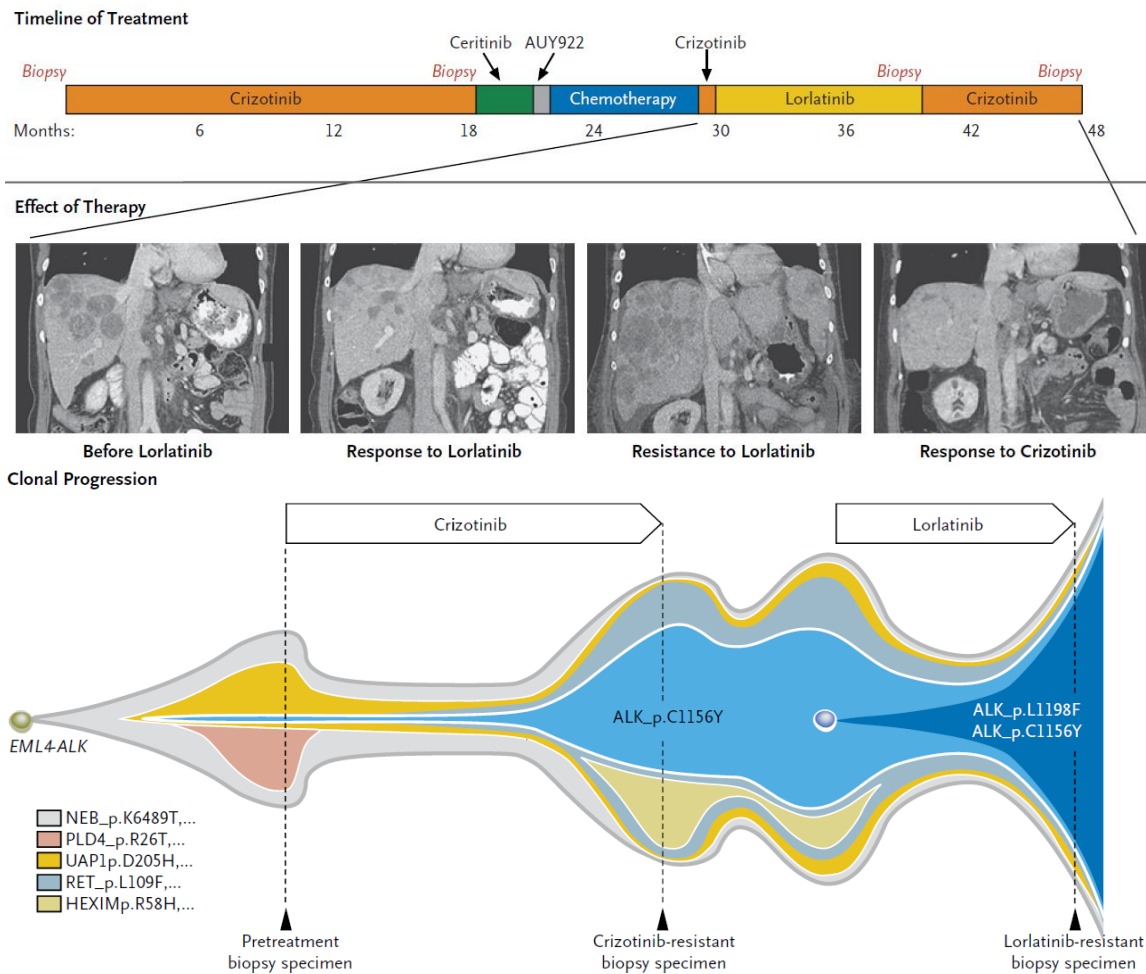
Three new 3<sup>rd</sup> generation ALKis (brigatinib, ensartinib and lorlatinib) have and are all undergoing comparative first line RCTs *versus* crizotinib. In particular, lorlatinib was developed specifically to have high penetration into the CNS and to target known resistance mechanisms (40). However, none of these studies are specifically addressing the question of drug resistance despite its inevitability. Therefore, what to do when ALKi treatment fails remains the key open question in the clinic.

Most recently we have shown in an expanded PII Trial that lorlatinib has substantial clinical activity in a broad range of clinical settings in *ALK+* NSCLC (2, 31)\*. Importantly, in patients having received several prior ALKIs, the ORR was 39%, with 48% ORR in CNS disease, but median PFS only 6.9 months (2)\*. Despite the activity confirmed by lorlatinib in pre-treated patients, most patients will be offered chemotherapy and/or supportive care, as lorlatinib is not currently registered in Australia, although it is FDA approved. The ALKternate clinical trial is examining the novel approach of alternating known effective drug therapy (lorlatinib and crizotinib) in patients with refractory, advanced *ALK+* NSCLC, aiming to identify and overcome drug resistance in order to prolong patient survival, which is very poor from this point in their diagnosis.

It remains unknown how-to best sequence ALKi therapy in the overall patient journey, to best delay drug resistance while also maintaining CNS disease control. Current therapeutic decision-making is empiric based on results from PIII front line trials. The point of difference for all the available agents may ultimately come through molecularly selected therapeutic decision making, with drugs chosen according to *ALK* KD resistance mutation profiles, as in the proposed *ALK* NSCLC sub-study in the NCI Master Protocol (NCT03737994). Obtaining data to guide such decision- making, both upfront and after prior ALKi therapy, is thus a large area of unmet need.

The recent landmark case report of an *ALK+* NSCLC patient who had multiple repeat biopsies at tumour progression on TKI therapy emphasizes the value of knowing the KD molecular profile in guiding therapeutic decision making (Figure 3). Thirty-six months in to treatment, in addition to the original crizotinib resistant C1156Y, the patient developed a new KD mutation (L1198F) associated with lorlatinib resistance. Remarkably, the patient was rechallenged with crizotinib and achieved a subsequent response due to expansion and dominance of sensitisation sub-clones (41). Next generation sequencing of ctDNA has since been used as a less invasive “liquid” biopsy which may predict for drug sensitivity or impending resistance (2).

In ALKternate the clinical utility of the molecular data generated from ctDNA/RNA and proteomic analyses of longitudinal plasma collections will be determined by correlating these results with clinical efficacy data. This novel strategy will determine whether markers of ALKi resistance emerge and are detectable in blood before clinical progression develops and how they alter with therapy.



**Figure 3.** shows the various ALKi the patient received as well as the duration of each treatment, the CT images of the patient’s metastatic liver disease through treatment including response to rechallenge with crizotinib. The below panel illustrates clonal evolution of resistance to ALK inhibitors in the patient after undergoing re-biopsy. A founder ALK C1156Y subclone was detectable at low frequency in the pre-treatment tumour specimen. With crizotinib therapy, this subclone expanded to 50% of the tumour cell population and led to the patient’s relapse. Lorlatinib was effective against the crizotinib-resistant tumour, but the C1156Y subclone acquired a second *ALK* mutation, L1198F. The double-mutant subclone (C1156Y– L1198F) was insensitive to lorlatinib and became the dominant subclone in the relapsed tumour (41).

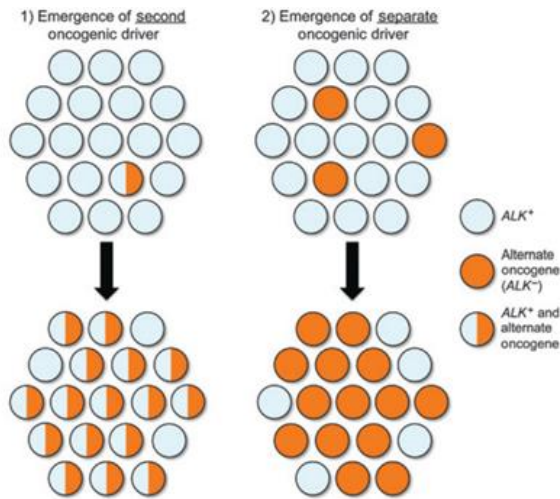
Such potential clonal evolution is demonstrated during therapy with different ALKi leading to dissimilar patterns of *ALK* KD mutations in re-biopsies from resistant patients. For example, over one third of patients, resistant to alectinib, have demonstrated the multi-ALKi resistant G1202R KD mutation (41). Of great interest, lorlatinib remains active in the presence of G1202R. Phase II lorlatinib data reported an attenuated PFS benefit in patients pre-treated with only a second generation inhibitor, as well as a deeper ORR both systemically and intra-cranially in those more heavily pre-treated (2).

Therefore, the ultimate objective in treating this molecularly unique sub-group of NSCLC is to delay or inhibit the emergence of KD mutations or alternate resistance mechanisms and sequence treatment both to promote superior prolonged response to current therapy *and* preserve potency of subsequent ALKi therapy when required. Extending OS is the most



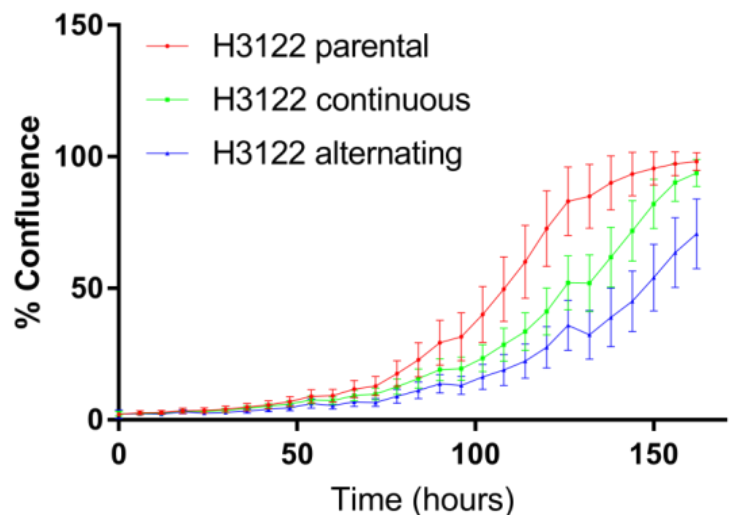
important endpoint and how best to do this with the currently available therapies remains an open question in clinical trials and in the real world.

The ALKternate Trial hypothesis is based on the principle that alternating ALKi therapy may preserve sensitivity to ALKis by selection pressure against the development of resistance mechanisms (Figure 4.). This is supported by the landmark case report described previously (Figure 3.) and by unpublished pre-clinical data (Figure 5.).



**Figure 4.** Diagrammatic representation of the effect of selection pressure with continuous drugging in enabling 1) the emergence of a second ALK-dominant oncogene driver and 2) the emergence of a second ALK-independent oncogene driver to explain treatment resistance (20)

**Figure 5.** Live cell proliferation assay, performed over 160 hours in the human H3122 ALK+ (variant 1) cell line. At the completion of the time-course, ceritinib-resistant subline treated with alternating ALKI (“H3122 alternating”, blue line) are less confluent compared to the parental (ceritinib sensitive, “H3122 parental”, red line) H3122 cells.



ALKternate is the first study in the world to address this hypothesis in ALK+ NSCLC, although at least two studies evaluating alternating drug therapy have been initiated in EGFR- mutated NSCLC. One of these, OSCILLATE (ACTRN 12617000720314), has completed accrual through the Australasian Lung Cancer Trials Group (42).

Reports in 2019 and 2020 have emerged to describe MET dysregulation as a frequent resistance mechanism to lorlatinib, in one series in 22%. Crizotinib is the only ALK-inhibitor with MET activity, as originally developed as a MET inhibitor. The rationale for short intermingled crizotinib in ALKternate is strengthened by this observation (43).

### 3 AIM AND OBJECTIVES

#### General aim(s)

The overarching aim of the ALKternate clinical trial is to investigate the fixed alternating schedule of lorlatinib (3<sup>rd</sup> generation ALKi) followed by crizotinib (1<sup>st</sup> generation ALKi) in pre-treated *ALK+* NSCLC patients who have progressed on 2<sup>nd</sup> generation ALKI therapy.

This study will determine the practical feasibility of this innovative schedule and the clinical utility of blood plasma to predict disease control or progression, with the eventual goal of establishing a new therapeutic strategy using already available drugs to increase survival for progressed *ALK+* patients who currently have no or very limited further options.

#### Hypothesis

Based on our knowledge of the differential patterns of resistance to different ALKis and supported by our unpublished and ongoing *in vitro* data, the underlying hypothesis for the ALKternate study is that ALKi-resistance mechanisms are either present at baseline or acquired through selection pressure from ALKi therapy and confer variable resistance to ALKis. Thus, it is hypothesised that treating *ALK+* NSCLC patients with alternating ALKis will suppress further clonal selection and drug resistance leading to longer disease control and increased survival for these patients who have progressed and have no limited options.

#### Primary Aims

To identify whether a fixed alternating schedule of lorlatinib followed by crizotinib followed by lorlatinib and so on is:

- Feasible and active, resulting in prolonged systemic and intracranial disease control delaying the emergence of ALKi resistance
- Safe, with a comparable toxicity profile to a continual dosing strategy

To determine whether a fixed alternating schedule of lorlatinib followed by crizotinib followed by lorlatinib and so on, will result in suppression of: ALK gene resistance KD mutations measurable in circulating tumour (ct) DNA; plasma proteomic drivers; or alternative oncogenic drivers and to explore post hoc whether this approach can be used to identify the development of resistance before progression is clinically and radiologically evident.

#### Secondary Aims

To explore ALK- genomic and proteomic resistance profiles in blood dynamically at regular fixed intervals of the fixed alternating drug schedule

To investigate whether the detection of ALK KD mutation profiles or alternate resistance drivers in the blood are a harbinger for clinical behaviour (response or progression)

### **Primary Objective**

To determine the time to treatment failure with alternating ALKi therapy (TTTF)\* defined as the time from alternating treatment initiation to treatment discontinuation (months) all cause and compare this to historical reports of continuous therapy (1). Only patients entering the alternating 'active' phase of the study will be analysed for the primary outcome  
\*TTTF defined in Section 4.6 p19

### **Secondary Objectives**

- TTTF for the whole cohort enrolled on trial (including those with progression on during induction phase i.e. primary lorlatinib resistance)
- Best objective response at any time of the study
- Progression free survival, PFS1 and PFS2 (if applicable)
- To determine the overall DCR (CR, PR, SD; systemic and CNS) % after 12 weeks lorlatinib induction and after the first cycle of alternating therapy and median
- Overall survival (OS)
- Safety/Toxicity assessment
- PROs/QOL measure analysis
- ctDNA and protein profiling for emergence of ALK kinase domain (KD) mutations and alterations in protein expression

## **4 DESIGN**

### **4.1 Overview**

This is an open label, single arm, proof of concept, multi-centre study, with clinical efficacy, safety and feasibility, as well as key translational outcomes measures. The trial schema is available in Figure 1.(p11).

### **4.2 Pharmacokinetics**

After oral administration of single dose crizotinib, peak plasma concentrations are reached at about 4 hours and followed by a multi-exponential decline with an average terminal half-life of 43 to 51 hours across doses.

After oral administration of single dose lorlatinib, peak plasma concentrations are reached at about 1-2 hours, with a mean plasma elimination half-life of lorlatinib after a single dose of 100 mg 20.9hours and supports once daily dosing.

Lorlatinib and crizotinib are both simultaneous inhibitors and inducers of CYP3A4. With continuous dosing, the net effect with crizotinib is auto-inhibition, whereas with lorlatinib it is auto-induction. Furthermore, inhibition will occur almost instantaneously, whereas induction will take ~ 7 days to maximize, and likewise persist > 7 days after the drug is stopped.

Therefore, the drug switch in this study will experience the lingering effects on the CYP3A enzyme from the prior drug the patient has received.

The intent of the PK collections in this study is to first confirm that exposures in this study are comparable to historical levels for the two drugs, and to also evaluate any lasting drug interaction between the two drugs.

Based on a detailed review of pharmacokinetic factors, blood will be drawn for PK analysis between cycle 1-2a and cycle 2a-2b at drug switch 1 and switch 2. Drug will be stopped 48 hours prior to the start of a new cycle and clinic visit for drug switch. PK bloods will be drawn at +1, 2, 4, 6 and 24 hours post initiating the new cycle drug.

<b>PK Plasma Collection (hours)</b>	<b>+1</b>	<b>+2</b>	<b>+4</b>	<b>+6</b>	<b>+24</b>
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Pharmacokinetic samples will be batched into two shipments, one from each site when fully recruited. PK analysis will be performed by Covance Inc. Shanghai China and will be analysed during the trial to ensure washout is as anticipated with minimal drug-drug interaction.

### 4.3 Radiologic Analysis

All imaging will be reported in keeping with RECIST 1.1 standard reporting practice (Appendix 2.) (45).

During Cycle 1 'Induction' and the first two alternating- Cycles 2 and 3, imaging will occur at shortened intervals (at each drug switch) detailed in Figure 1. and Section 11, before occurring 12-weekly thereafter.

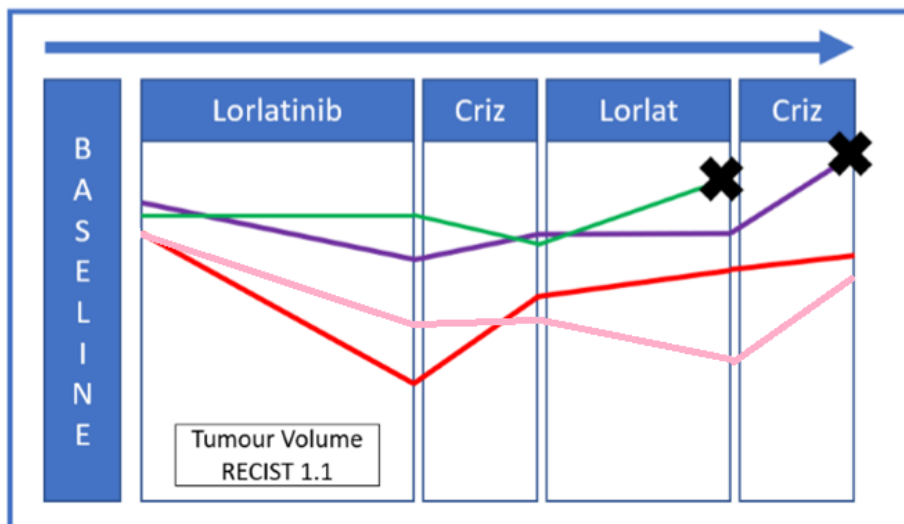
Disease progression is defined according to RECIST 1.1 (Appendix 2.) when a patient is on lorlatinib for both intra and extra-cranial lesions, and for crizotinib for intra and extracranial lesions, **however** for extra-cranial lesions disease control measure will be modified IF meeting RECIST 1.1 progressive disease criteria, and assessed by the investigator based on **direct** comparison back to the baseline imaging. See Figure 6. below for further explanation.

Crizotinib is being used in this setting to prevent the emergence of resistant clones to lorlatinib (41), however, any mutational shift enabling re-sensitisation to crizotinib will also be investigated (post hoc). A patient is deemed stable on crizotinib if their non-CNS RECIST 1.1 measurable target lesions are **at least** stable compared to baseline imaging AND their CNS lesions if applicable are stable as per standard RECIST 1.1.

Lorlatinib and crizotinib can be **continued at progression** at investigator discretion provided

- the patient is felt to be clinically benefiting AND
- the sites of disease progression are considered not clinically significant OR
- where they are new and not considered clinically significant, OR they are isolated and treatable with local means e.g. radiotherapy (SBRT).

Patients with clear disease progression (RECIST 1.1) considered clinically significant by the investigator will come off the study (See section 9.2 for complete criteria).



**Figure 6.** Four examples with differing tumour measurements by RECIST 1.1. All four patients maintain disease control on induction lorlatinib and are eligible to proceed on to alternating therapy. Based on imaging, the red patient can remain on the alternating arm of the trial provided they are asymptomatic. The purple patient has progressed on crizotinib with total tumour volume greater than at baseline, the green patient has progressed on lorlatinib. The pink patient has progressed on crizotinib via RECIST 1.1 extra-cranially, however has not progressed when compared back to baseline imaging and may continue on alternating therapy without meeting progression criteria. IF the pink patient had progressed via RECIST 1.1 intra-cranially, they may continue on alternating therapy if deemed appropriate, however as ‘treatment beyond progression’. The purple and green patients must be reviewed by the TMC and may be eligible for **‘treatment beyond progression’**, as per Section 9.2p53 TMC’s discretion.

#### 4.4 Multi-Omic Pathological Analysis

Blood will be collected for ctDNA and protein analysis at baseline, at Cycle 2a, 2b, 3a, 3b, then 12 weekly thereafter until disease progression. Longitudinal blood and tissue profiling in addition to comprehensive imaging to identify novel predictive biomarkers of therapy response and resistance. Moreover, it will also explore novel blood based proteomic profiling to identify protein markers of resistance. Blood will be collected into 10 mL cell-free DNA collection tubes, for NGS analysis and proteomic analysis to preserve the integrity of the cell free nucleic acids and proteins respectively. Samples will be centrifuged and plasma stored at -80°C until analysis.

Tumour tissue will be collected at baseline and upon disease progression from patients in whom it is safe and feasible to biopsy a site of disease, as deemed by the investigator in collaboration with the local interventional radiologist. Matched resistance profiles with corresponding blood samples will be performed and references to the patients archival diagnostic tissue sample (FFPE) where possible.

#### **4.5 Toxicity and Patient Reported Outcome Analysis**

Patient assessment of safety and tolerability will be implemented utilising standardized validated tools will be implemented including the FACT-L patient reported outcome lung cancer assessment tool (Appendix 3.), and the CTCAE version 4.3 (Appendix 4.). This will be complemented with clinical history, examination, cognitive assessment (MiniCog), standard blood test results and ECG scheduled reviews.

#### **4.6 Definition of Time to Treatment Failure**

TTTF is defined as the **time** in months from alternating treatment initiation to alternating **treatment** discontinuation for any reason at investigator discretion, including disease progression, **treatment** toxicity, patient preference, clinical deterioration or death. Disease progression/control criteria, at the discretion of the investigator. TTTF will be measured only in those who enter the alternating phase of the study and analysis will include those whom have been treated beyond progression on ongoing alternating therapy.

### **5 SUBJECT POPULATION**

#### **5.1 Target Population**

Advanced, inoperable, pre-treated ALK gene rearranged NSCLC having received any number of prior lines of ALKi therapy and chemotherapy, with the most recent ALKi being a second generation ALKi (eg. ceritinib, entrectinib, alectinib or brigatinib). Patients previously treated with third generation ALKi are not eligible.

##### **5.1.1 Inclusion criteria**

- Adults aged  $\geq 18$  years with pathologically confirmed stage IV ALK gene rearranged NSCLC (predominantly adenocarcinoma phenotype) by an accepted local pathology diagnostic platform, fresh or archival, not required to be reconfirmed centrally
- Confirmed radiological disease progression on prior second generation ALKi as per RECIST Version 1.1
- Any prior number of lines of systemic therapy, provided the most recent ALKi was a second generation agent
- Extra-cranial RECIST measurable disease confirmed  $\leq 28$  days prior to start of study
- Eastern Co-operative Oncology Group (ECOG) performance status  $\leq 1$
- Patients with asymptomatic CNS disease including leptomeningeal disease or CNS only progression are eligible
- Patients with symptomatic CNS disease including leptomeningeal disease are eligible if treated with local therapy(ies) including surgery and or radiotherapy and stable clinically with stable steroid requirements for  $\geq 14$  days

- Adequate bone marrow function (e.g. platelets > 100 x 10<sup>9</sup>/L, ANC ≥ 1.5 x 10<sup>9</sup>/L, Hb ≥90)
- Adequate liver function (e.g. ALT/AST < ≤ 3 x ULN; if liver metastases ≤ 5 x ULN, bilirubin ≤ 2 x ULN)
- Adequate renal function (e.g. creatinine clearance ≥ 50 ml/min, serum creatinine ≤ 1.5 x ULN)
- Study treatment both planned and able to start within 14 days of consent
- Willing and able to comply with all study requirements, including treatment (e.g. able to swallow tablets), timing and/or nature of required assessments (e.g. able to have IV contrast if this is required for tumour assessments)
- Signed, written informed consent (for trial inclusion and tissue collection)
- Prior screen failure patients are eligible for rescreening

### 5.1.2 Exclusion criteria

- Most recent systemic treatment is crizotinib
- Prior hypersensitivity to crizotinib
- Primary resistance to first line ALKi therapy (first or second generation ALKi)
- Prior lorlatinib therapy or other third generation ALKi therapy
- Prior toxicity to crizotinib contraindicating further use
- Previous ALKi therapy within 4 days, or chemotherapy or radiotherapy within 7 days
- Specific comorbidities or conditions affecting compliance to clinical trial
- Life expectancy of less than 3 months
- Inability to tolerate or contraindication to MRI-B imaging
- No measurable disease via RECIST v1.1 criteria extra-cranially
- Significant cardiac dysfunction
- Untreated and or non-clinically stable symptomatic CNS including leptomeningeal disease
- Past history of malignancy except the following whom are eligible: adequately treated carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial transitional cell carcinoma of the bladder, or curatively treated cervical carcinoma in situ. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment, with the exception of men with prostate cancer, eligible if PSA and radiological control for at least 2 years
- Significant uncontrolled infection, including chronic active hepatitis B, hepatitis C, or HIV.
- Concurrent illness, including severe infection that may jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety
- The requirement to continue one of the excluded concomitant medications (Section 8.6) - administration of strong CYP3A inducers (e.g., carbamazepine, mitotane, phenytoin, rifampin, St. John's Wort) is not permitted within 12 days before the first lorlatinib dose
- Serious medical or psychiatric conditions that might limit the ability of the patient to comply with the protocol
- Comorbid malabsorption syndrome or other gastrointestinal (GI) illness or condition that could affect oral absorption of the study drug

- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse.
- Pregnancy, lactation, or inadequate contraception. Women must be post-menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to Cycle 1 Day 1. Men must have been surgically sterilised or use a (double if required) barrier method of contraception.
- An inability to travel to the enrolled site to participate in the trial and all required visits

### **5.1.3 Criteria for Progression into the Alternating Arm**

- Disease control intra and extra-cranially after continuous lorlatinib induction cycle
- Unresolved significant adverse events to lorlatinib during induction are a contraindication to its ongoing use

## **6 STUDY ENROLLMENT**

### **6.1 Screening**

Written informed consent must be signed and dated by the subject and investigator, prior to any study-specific screening investigations being performed.

Entry to this study is conditional on confirmation of tumour ALK status by means of mutation analysis performed on representative samples of diagnostic tumour tissue by the local accredited laboratory. Archival tumour samples are acceptable for ALK mutation analysis. Confirmation of the report via IHC and or FISH or NGS are sufficient to confirm ALK positivity. If a patient is deemed safe to undergo the mandatory baseline biopsy for trial entry, FFPE preparation of the biopsy with confirmation of histology (adenocarcinoma predominate) and ALK IHC are required prior to first dose.

Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory manual.

### **6.2 Study Enrollment**

Once a participant consents to the trial, they will be assigned a participant study number. Individuals may only be assigned one study number in this trial.

Participants should only be enrolled after all screening assessments have been performed and the responsible investigator has verified the participant's eligibility, with all inclusion criteria met and none of the exclusion criteria. No exceptions will be made to these eligibility requirements at the time of trial enrolment.

All enquiries about eligibility should be addressed by contacting the Chief Investigators (CIs) and/or Trial Management Committee (TMC) prior to enrolment. The TMC will consist of the trial clinical leads and project manager. There is no external TMC body for this trial.



Study treatment must be planned to start within **14** days of patient consent, however if screening assessments are not completed within the 14 day screening period, patients can sign a new consent form to extend this screening period by another 14 days. Patients who are re-screened will use their original study number.

## 7 TREATMENT PLAN

### 7.1 Drug Supply and Accountability

#### Lorlatinib

Lorlatinib will be supplied by Pfizer as 25mg tablets for oral administration as a once daily dose of 100mg. Each pack will contain 30 tablets of lorlatinib in 30ct bulk unlabelled bottles with an ink jet code identifier and will be labelled by external facility PCI Port Melbourne prior to distribution to both sites.

The 25mg tablets can then be used when dose modification is required for toxicity/adverse event management, see Section 7.5.4.

Unopened packs of lorlatinib tablets must be stored at approximately 25°C (77°F). Lorlatinib must be used within the individually assigned expiry date on the label.

#### Crizotinib

Crizotinib will be supplied by Pfizer as tablets for oral administration as a twice daily dose of 250mg. Each pack will contain 60 tablets of crizotinib.

Pfizer will supply 200mg tablets for dose reduction if required, see Section 7.5.4,

Unopened packs of crizotinib tablets must be stored at approximately 25°C (77°F). Crizotinib must be used within the individually assigned expiry date on the label.

### 7.2 Administration of Study Treatments

All participants will receive:

Phase	Drug	Dose	Route	Duration
Induction	Lorlatinib	100mg OD	PO	12 weeks (1 cycle = 12 weeks)
Alternating*	Crizotinib	250mg BID	PO	Alternating between 4 weeks of crizotinib, then 8 weeks lorlatinib (e.g. 1 cycle = 12 weeks), followed by a repeating cycle of 4 weeks of crizotinib and 8 weeks of lorlatinib and so on until disease progression or unacceptable toxicity
	Lorlatinib	100mg OD	PO	
Post-progression	Lorlatinib	100mg OD	PO	*Until further progression or prohibitive toxicity

\* After the participant progresses radiologically or develops a dose limiting toxicity to crizotinib, continuous dosing with lorlatinib may be permitted after consultation with the CIs and delegates of the TMC.

Lorlatinib 100mg OD will be taken from Cycle 1 in the mornings with food and water for 12 weeks. Patients will take their last dose of lorlatinib 48 hours prior to switching over to crizotinib in Cycle 2a. In cycle 2a, crizotinib 250mg will be taken twice daily (BD) with food and water for 4 weeks, with their last dose on the evening of Day 26, allowing for a 48 hour break prior to switching back to lorlatinib in Cycle 2b. Lorlatinib will be taken OD in the mornings with food and water for 8 weeks. Patients will continue alternating between crizotinib for 4 weeks (i.e. Cycle 3a, 4a, etc) followed by lorlatinib for 8 weeks (i.e. Cycle 3b, 4b, etc) and so on, with a 48 hour break prior to each drug switch.

### **7.3 Required Background Treatment**

There is no required background medication or premedication for lorlatinib and crizotinib.

### **7.4 Administration of Treatment**

Both lorlatinib and crizotinib are administered preferably with food and water. Patients should remain upright for 30 minutes after taking study medication. Alternatively, in special circumstances, a fasted state is acceptable.

### **7.5 Dose Modifications**

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Patients will be monitored closely for toxicity and the dose of crizotinib or lorlatinib may be adjusted as indicated in Section 7.5.3 and 7.5.4 (below). Intra-patient dose reduction by 1 and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered (Dose Level -1 for crizotinib is 200 mg BID; Dose Level -2 is 250 mg QD). Patients requiring more than 2 dose reductions due to treatment-related toxicity are not allowed, and the patient will discontinue on the study.

#### **7.5.1 Dose Delay for Adverse Events**

Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs, upon clinical judgment of the investigator. Adverse events are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix 3.).

Study drug administration may be delayed for up to 28 days to allow for improvement or resolution of the event. If an AE does not resolve to Grade 1 or less after dose interruption for more than 28 days, the CIs of the TMC must be re-contacted. Comprehensive assessments of any study drug-related AEs (i.e., adverse drug reactions) experienced by

the patient will be performed throughout the course of the study. Dose delays beyond 28 days may be permitted following approval by the TMC in special circumstances, provided the dose delay is not attributable to drug related adverse events. Patients who resume drug after dose delay will continue as per scheduled treatment, unless otherwise advised by the TMC.

Instructions for treatment delays and dose modifications for adverse events are specified below.

**In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until the adverse event has resolved to G0-1, at the investigator's discretion.**

The severity of the event, as well as clinical judgment, will be utilised to determine appropriate management of the patient for any AE experienced while participating in this study. Any medication, including those administered for therapy of symptoms considered associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF.

### 7.5.2 Dose Levels

Drug	Units	Starting Dose	Level		
			0	-1	-2
Lorlatinib	mg	100 OD	100	75	50
Crizotinib	mg	250 BID	250/250	200/200	250

### 7.5.3 Dose Modifications for Adverse Events

If a patient experiences a CTCAE  $\geq$  grade 3 and/or an unacceptable toxicity of any grade, where the investigator considers the event of concern to be specifically associated with the trial medications (and not attributable to the disease or disease-related process for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to CTCAE grade  $\leq$  1 within 4 weeks of onset, then that study drug may be later restarted, when due, at either the same dose (e.g. crizotinib 250mg BID) or a lower dose (crizotinib 200mg BID) using the rules below in Table 1, as per the investigator's evaluation and discussion with delegates of the TMC.

Reimaging can be delayed in the setting of drug delay up to a limit of 2 weeks, if the delay is longer, reimaging should resume at or within 2 weeks. If appropriate, ongoing imaging may resynchronise with the original imaging time point schedule for subsequent cycles.

**Once a dose reduction is implemented, the dose can be re-escalated if deemed appropriate.**

The dates of the cycles will be delayed i.e. if a dose interruption occurs on day 22 of a lorlatinib cycle, and the patient is able to reconvene 10 days later, they will re-enter at day 32 of lorlatinib, the same cycle.

If a treatment-related adverse event does not resolve to CTCAE grade 0- 2 within 4 weeks, then permanent discontinuation from study treatment should be considered after discussion with delegates of the TMC. Participants should be followed until the resolution of toxicity due to study treatment. Any change from dosing schedule or dose interruptions must be recorded in the (e)CRF.

### 7.5.4 Table 2 Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities (4)

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Pancreatitis	N/A	<p>If elevated enzymes (both amylase and lipase are Grade <math>\leq 2</math>) are observed in the absence of radiological findings of pancreatitis: continue lorlatinib at the same dose level without dose hold. Repeat lipase and amylase and obtain pancreatic isoenzyme if possible.</p> <p>If radiologically confirmed pancreatitis: withhold lorlatinib dose. Repeat radiology and lipase and amylase weekly and obtain and amylase are Grade <math>\leq 2</math>. pancreatic isoenzyme. If appropriate, resume lorlatinib treatment at one dose level lower if radiology has returned to baseline and lipase</p>	Permanently discontinue lorlatinib	Permanently discontinue lorlatinib.
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Asymptomatic, radiographic findings only: No need for lorlatinib dose adjustment. Initiate appropriate monitoring.	Withhold current lorlatinib dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume lorlatinib treatment at one dose level lower. Discontinue lorlatinib permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Electrocardiogram QTc prolongation (see 8.7)	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue lorlatinib at the same dose level.	<p>Assess electrolytes and concomitant medications.</p> <p>Correct any electrolyte abnormalities, or hypoxia.</p> <p>Continue lorlatinib at the same dose level.</p>	<p>Withhold lorlatinib dose.</p> <p>Assess electrolytes and concomitant medications.</p> <p>Correct any electrolyte abnormalities, or hypoxia.</p>	Permanently discontinue lorlatinib.

			Upon recovery to Grade $\leq 1$ resume lorlatinib treatment at one dose level lower.	
LV Dysfunction	CTCAE v4.03 does not report Grade 1.	CTCAE v 4.03 does not report Grade 2.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Non-Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade $\leq 1$ (or has returned to baseline) then reduce the dose by 1 level or rechallenge at the same dose*.	Withhold dose until toxicity is Grade $\leq 1$ (or has returned to baseline), then reduce the dose by 1 level* or discontinue at of the the discretion investigator.
Mood and Cognitive Disturbance	Continue lorlatinib at the same dose level and monitor closely. Discuss supportive non-pharmacologic and pharmacologic intervention should symptoms	Reduce lorlatinib by one dose level. Investigate reversible causes and consider mood stabilising supportive non-pharmacologic and pharmacologic intervention.	Withhold lorlatinib dose until toxicity is Grade $\leq 1$ (or has returned to baseline) and dose reduce by one dose level. Review supportive non-pharmacologic and pharmacologic measures.  If recurrent, repeat the above. Further dose reduction and the	Withhold lorlatinib dose until toxicity is Grade $\leq 1$ (or has returned to baseline) and restart at two dose levels down.  If recurrent $\geq$ Grade 3, despite maximising supportive measures, permanently discontinue lorlatinib.  If recurrent $<$ Grade 3, withhold lorlatinib until

	persist or worsen.		discretion of the Investigator/TMC.	toxicity is ≤Grade 1, optimise supportive measures, and ongoing dose and continuation at the discretion of the Investigator.
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\* Patients who develop asymptomatic Grade 4 hyperuricaemia or Grade 3 hypophosphataemia may continue lorlatinib without dose modification at the discretion of the investigator. Nausea, vomiting or diarrhoea must persist at Grade 3 or 4 despite maximal medical therapy to require lorlatinib dose modification.

\*\* In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

§ If a patient has a potential diagnosis of pneumonitis or drug-related lung injury the same evaluations/procedures provided in Section 7.5.4.4 should be considered to assist or exclude the diagnosis of pneumonitis during this period.

### Hematologic Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade ≤1 (or has returned to baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.	Withhold lorlatinib dose until toxicity is Grade ≤1 (or has returned to baseline) then rechallenge at the same dose or reduce the dose by 1 dose level.

Lymphopaenia	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at the same dose; otherwise, withhold dose until toxicity is Grade $\leq$ 1 (or baseline) then rechallenge at the same dose or reduce by 1 level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at same dose; otherwise, withhold dose until toxicity is Grade $\leq$ 1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.
<b>Lipid Elevation Toxicities<sup>a</sup></b>				
Cholesterol	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid lowering agent or change to a new agent. Either continue lorlatinib at the same dose without interruption or withhold dose until toxicity is Grade $\leq$ 2 and then continue at the same dose.	Increase the dose of the statin or other lipid-lowering agent, or change to a new statin/lipid lowering agent. Withhold lorlatinib dose until toxicity is Grade $\leq$ 2 and then reduce the dose by 1 dose level or rechallenge at the same dose.



Triglycerides	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid-lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid-lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid-lowering agent or change to a new agent. Either continue lorlatinib at the same dose without interruption or withhold dose until toxicity is Grade $\leq 2$ and then continue at the same dose.	Increase the dose of the statin or other lipid-lowering agent, or change to a new statin/lipid-lowering agent. Withhold lorlatinib dose until toxicity is Grade $\leq 2$ and then reduce the dose by 1 dose level or rechallenge at the same dose.
<sup>a</sup> See also instructions provided in Section 7.5.4.1 Hyperlipidaemia.				

### 7.5.4.1 Hyperlipidaemia

In the lorlatinib Phase 1 Study B7461001, hypercholesterolaemia was the most common AE reported. Elevations in lipids usually begin in the first few cycles and, if statins are not introduced, can rise to Grade 3 levels by the next treatment cycle. Therefore, the suggested management is to begin a statin for Grade 1 elevations in either cholesterol or triglycerides and to increase the statin dose if adequate control is not obtained, as outlined in Table 2.

Members of the statin class of agents are differentially sensitive to CYP3A4, and **caution should be exercised when selecting statin for management of elevated lipid levels.**

Rosuvastatin can be used during lorlatinib treatment without dose adjustment since there is no CYP3A4 involvement in their elimination. Pravastatin, fluvastatin and atorvastatin should be used with caution during lorlatinib treatment, and a dose adjustment of these statins may be necessary (**increasing dose may be considered**). Lovastatin and simvastatin are not recommended for use during lorlatinib treatment.

### 7.5.4.2 PR Interval Prolongation

Analysis of ECG data from ongoing and completed human studies with lorlatinib has identified a subset of patients who exhibited ECG evidence of PR interval prolongation. The ECG changes appear limited to the PR interval with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies as described in the current lorlatinib IB.

Guidance for management of PR interval prolongation is provided in Table 3. below and examples of drug with potential PR interval prolongation effect can be found in Appendix 5.

**Table 3. PR Interval Prolongation Management**

	<b>First Occasion and Asymptomatic</b>	<b>Second Occasion and/or Symptomatic</b>
1 <sup>st</sup> -Degree Heart Block (PR interval >200 msec)	<b>No dose hold or reduction needed.</b> Assess concomitant medications. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if symptoms develop that may be related to heart block.	<b>Withhold dose.</b> Assess concomitant medications. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at same dose or consider dose reduction when symptoms resolve.

2 <sup>nd</sup> -Degree Heart Block	<b>Withhold dose.</b> Assess concomitant medications. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at same dose or consider dose reduction if subsequent ECG does not show 2nd degree block.	<b>Withhold dose.</b> Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree block resolves. If patients revert to 1st degree block with no symptoms, resume at reduced dose.
Complete Heart Block	<b>Withhold dose.</b> Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose. If no pacemaker placed, permanently discontinue lorlatinib.	

### 7.5.4.3 Assessment of Mood and Cognition

An assessment of mood will be administered to patients via the Beck Depression Inventory-II scale at the time points described in the Schedule of Activities (10.1 p52) and cited in Appendix 6. This is a 21- item self-report scale, with each item rated by patients on a 4-point scale (ranging from 0 -3). The scale includes items capturing mood (loss of pleasure, sadness, irritability), suicidal ideation, and cognitive signs (punitive thoughts, self- criticism, self-dislike, pessimism poor concentration) as well as somatic signs (appetite, sleep, fatigue, libido). Based on the scoring system, appropriate dosage change, additional treatment and referral to a psychiatric service should be arranged as appropriate.

A mini-COG will also be performed at regular intervals from baseline, and as described in the Schedule of Activities (10.1 p52), Appendix 8. In conjunction with the clinical history and global assessment, appropriate dose adjustment and modification should be made should the score trend down indicating diminished cognition.

**7.5.5 Table 4. Crizotinib Dose Modifications for Crizotinib-Related Toxicity (44)**

<b>Toxicity</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
ALT elevation possibly related to crizotinib with total bilirubin <2 X ULN.	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level. Obtain repeat ALT and total bilirubin when symptomatic or within 7 days.  §Country-specific guidelines may also apply.	Withhold crizotinib dose until toxicity is Grade ≥1, or has returned to baseline, then resume treatment by reducing by one dose level. If Grade 3 ALT elevation recurs reduce further (at most by 2 dose levels from the initial dose level). If recurrence at dose level -2, then discuss with sponsor whether or not to discontinue permanently. If ALT elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level. Country-specific guidelines may also apply.	See Grade 3 Country-specific guidelines may also apply.
ALT elevation and total bilirubin elevation ≥2X ULN (in absence of cholestasis or haemolysis).	Continue crizotinib at the same dose level. Obtain repeat ALT and total bilirubin within 48 hours.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.
Bradycardia (heart rate less than 60 beats per minute) See also instructions in	Continue crizotinib at the same dose level.	Withhold crizotinib until recovery to Grade ≤1 or to heart rate ≥60.  Evaluate concomitant medications known to cause bradycardia, as	Same as for Grade 2 bradycardia.	Permanently discontinue crizotinib if no contributing concomitant medication is identified.  If contributing concomitant medication

		<p>well as anti-hypertensive medications.</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at previous dose upon recovery to Grade <math>\leq 1</math> or to heart rate <math>\geq 60</math>.</p> <p>If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume crizotinib at reduced dose upon recovery to Grade <math>\leq 1</math> or to heart rate <math>\geq 60</math></p>		<p>is identified and discontinued, or its dose is adjusted, resume crizotinib at 250 mg once daily upon recovery to Grade <math>\leq 1</math> or to heart rate <math>\geq 60</math>, with frequent monitoring Permanently discontinue crizotinib for recurrence.</p>
<p>Pneumonitis (not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect). See also instructions in <a href="#">Section 7.5.5.4</a></p>	<p>Discontinue crizotinib treatment and do not retreat.</p>	<p>Discontinue crizotinib treatment and do not retreat.</p>	<p>Discontinue crizotinib treatment and do not retreat.</p>	<p>Discontinue crizotinib treatment and do not retreat.</p>

<b>Toxicity</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Left ventricular systolic dysfunction.	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.
Electrocardiogram QTc prolongation.	Continue crizotinib at the same dose level.	Assess electrolytes and concomitant medications Correct any electrolyte or magnesium abnormalities Continue crizotinib at the same dose level.	Interrupt crizotinib until recovery to Grade $\leq 1$ . Assess and correct electrolytes and concomitant medications. Upon recovery to Grade $\leq 1$ , resume crizotinib treatment by reducing the dose by one dose level if no other cause for QTc prolongation is found otherwise resume crizotinib at the same dose level.	Discontinue crizotinib treatment and do not retreat.
Vision disorders	Continue crizotinib at the same dose level Repeat ophthalmologic consultation.	Continue crizotinib at the same dose level Repeat ophthalmologic consultation.	Interrupt crizotinib until recovery to Grade $\leq 1$ . Repeat ophthalmologic consultation <sup>‡</sup> Resume crizotinib treatment by reducing the dose by one dose level upon recovery to Grade $\leq 1$ .	Discontinue crizotinib and do not retreat. Repeat ophthalmologic consultation.
Non-Hematologic General (excluding those mentioned above).	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Withhold crizotinib dose until toxicity is grade $\geq 1$ , or has returned to baseline, then resume crizotinib treatment at the same dose or reduce the dose by 1 level at the discretion of the investigator*.	Withhold crizotinib dose until toxicity is grade $\leq 1$ , or has returned to baseline, then reduce crizotinib dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*.

<b>Toxicity</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Hematologic (excluding lymphopaenia <sup>†</sup> ).	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Withhold crizotinib dose until toxicity is grade $\geq 2$ , or has returned to baseline, then resume crizotinib treatment at the same dose level or reduce the dose by 1 dose level after discussion with the sponsor. <sup>†</sup>	Withhold crizotinib dose until toxicity is grade $\leq 2$ , or has returned to baseline, then reduce the crizotinib dose by 1 level and resume treatment <sup>†</sup> .

\*Patients who develop Grade 4 hyperuricaemia or Grade 3 hypophosphataemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

†Patients who develop Grade 3 or 4 lymphopaenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

Ophthalmologic examination includes visual acuity, fundoscopy, and slit lamp, biomicroscopy and should be performed by an ophthalmologist. Ophthalmologic examinations should be repeated during the study whenever a vision disorder AE is observed or NCI -CTCAE v 4.3 grade change occurs from the previous visit.

Patient management of increased ALT  $>3 - \leq 5$  x ULN (Grade 2) with a total bilirubin  $<2$  x ULN will be discussed on a case-by-case basis between the CIs and TMC and determine whether to: a. Continue treatment at the same dose level of crizotinib; b. Withhold crizotinib until ALT is Grade  $\leq 1$  or has returned to baseline, then resume treatment at the same dose level; or c. Withhold crizotinib until ALT is Grade  $\leq 1$  or has returned to baseline, then reduce the dose by 1 dose level.

### 7.5.5.1 Nausea and Emesis

For nausea and emesis with crizotinib, treat with standard antiemetics as per institutional standard practice. Taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered.

### 7.5.5.2 Diarrhoea

Grade 1: Symptomatic care with anti-diarrheal medication (such as loperamide), or no intervention as per investigator judgment.

Grade 2: Loperamide (4 mg at first onset, then 2 mg every 2 to 4 hours until symptom-free for 12 hours). Other anti-diarrheal medications can be used per local standard-of-care. No dose modification unless patient is intolerant or symptom is recurrent.

Grade 3-4 (despite use of anti-diarrheal medication such as loperamide): Withhold crizotinib (or lorlatinib) treatment until recovery to Grade  $\geq 1$ .

### 7.5.5.3 Bradycardia

Avoid using crizotinib in combination with other bradycardic agents (eg, beta blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia.

### 7.5.5.4 Pneumonitis/Pneumonia

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, then the following evaluations/procedures should be considered to confirm or exclude the diagnosis of pneumonitis during this period in the absence of disease progression, other pulmonary disease, infection, or radiation effects:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria;
- Blood culture should be performed in febrile patients. Consider appropriate serologies (mycoplasma, legionella, cytomegalovirus, other viruses, etc.);
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology);
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture, microbiology, and cytology (same pathogens as above);
- Lung biopsy, if appropriate;
- A plasma sample for BNP (B-type natriuretic peptide) to evaluate for evidence of congestive heart failure (CHF);
- A blood sample for  $\beta$ -D glucan to evaluate for the presence of fungal pneumonia (e.g., *Pneumocystis jirovecii*)



If clinically appropriate, high-dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis.

For any case of drug-related pneumonitis, discontinue crizotinib and contact the TMC immediately.

#### **7.5.5.5 Renal Cysts**

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Active surveillance with appropriate imaging (contrast-enhanced CT scanning or MRI) should be performed at the time of the renal cysts diagnosis. Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

In addition, multitest dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter.\*

Urine reflex microscopy is required whenever urine multi-test dipstick is positive for blood or protein and/or if this is the local standard.

\*Additional analysis per local requirement may be performed.

#### **7.5.5.6 Severe Visual Loss**

Discontinue crizotinib in patients with severe visual loss (best corrected vision less than 20/200 in one or both eyes).

Any adverse event of Grade  $\geq 2$  of potential sight threatening (PST) or severe vision loss (SVL) that occurs in crizotinib treated patient should be treated as SAEs (Serious Adverse Events) regardless of relatedness to study drug (except for visual field defect, for which only Grade  $\geq 3$  should be treated as SAE).

## **8 CONCOMITANT TREATMENTS**

### **8.1 Recommended**

It is recommended, given moderate emetogenicity, patients have metoclopramide PO 10mg PRN, TDS prescribed (orally, as required, up to three times daily).

Live vaccines are not allowed during treatment.

## **8.2 Radiotherapy or Surgery**

No other systemic anti-cancer therapies (including chemotherapy, hormonal treatment [except corticosteroids and megestrol acetate], antibody or other immunotherapy, or other experimental drugs) of any kind will be permitted while the patient is participating in the study.

Palliative radiotherapy or local surgical treatment to specific sites of disease is permitted if considered medically necessary by the treating physician and there is no disease progression. All attempts should be made to rule out disease progression in the event of increased localised pain. If the palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression. All procedures performed (e.g. radiotherapy, surgery, thoracentesis, etc.) undertaken during the study must be documented in the patient's medical record.

Stereotactic radiotherapy or radiosurgery may be performed to asymptomatic 'oligo-progressive' disease defined as 1-2 non-critical extra-cranial sites, and 6 or less CNS sites provided all other criteria in Section 9.2p53 are met and the patient is being 'treated beyond progression'.

Crizotinib and lorlatinib treatment may be interrupted during radiotherapy however is not mandated to be – stopping 1 day before and resuming treatment 1 day after or at the discretion of the treating team if further concern for radiosensitisation based on the field being treated.

The effect of crizotinib and lorlatinib in wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential anti-angiogenic effect). In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

## **8.3 Haematopoietic Growth Factors and Blood Products**

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Prophylactic use of these agents is not permitted.

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

## **8.4 Other Concomitant Medications**

Therapies considered necessary for patients' well-being may be given at the discretion of the investigator. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary

therapies should not be encouraged because of unknown side effects and potential drug interactions.

Medications specifically prohibited in the Exclusion Criteria may not be allowed during the active treatment period.

If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from study therapy or medication may be required. The final decision on any supportive therapy rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication schedule requires the mutual agreement of the Investigator, the sponsor, and the patient.

Concomitant medications and treatments will be recorded from 14 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (e.g. antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g. transfusions).

Medications intended solely for supportive care (eg, antiemetics, analgesics, megestrol acetate for anorexia, bisphosphonates or RANK-ligands for metastatic bone disease or osteoporosis) are allowed. In case the patient is already on treatment with RANK-ligands (like denosumab) before study entry, the therapy should be at a stable dose prior to randomization.

There are no prohibited therapies during the Post-Treatment Follow-Up Phase.

## **8.5 Inhibitors and Inducers of CYP Enzymes**

The list of food and drugs to be avoided provided below may not be fully exhaustive. Consult the manufacturer when in doubt whether a food or a drug falls into any of the categories below.

### **8.5.1 Lorlatinib**

The *in vitro* studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of lorlatinib, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

Initial *in vitro* assessment for inhibition and induction drug-drug interaction potential indicated that lorlatinib is a time-dependent inhibitor of CYP 3A and also an inducer of CYP3A and CYP2B6. The net effect of lorlatinib on CYP3A is currently under investigation. At substantially higher concentrations than those observed clinically, lorlatinib also inhibited CYP2C9 in *in vitro* studies.

Coadministration of strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) **is not permitted within 12 days before the first lorlatinib dose and until the last lorlatinib dose.** Caution should

be exercised when coadministering drugs that are moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, and nafcillin).

Caution should be exercised when co-administering drugs that are sensitive CYP2B6 substrates such as bupropion and efavirenz. The safety of the drug should be closely monitored and the dose could be adjusted if necessary.

Coadministration of lorlatinib with CYP3A substrates with a narrow therapeutic index, such as alfentanil, astemizole,\* cisapride,\* cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozone, quinidine, sirolimus, tacrolimus, terfenadine\* (\*withdrawn from US market) is not permitted starting from the first lorlatinib dose and until the completion of the first 14 days of lorlatinib dose. Alternate medications should be considered.

The use of a CYP3A substrate with narrow therapeutic index is not recommended during lorlatinib treatment on study, but if it is absolutely necessary to use, the dose of the CYP3A substrate may need to be increased. If there is a change in the lorlatinib dosing regimen such as a dosing interruption or dose reduction, the administration of the CYP3A substrate with narrow therapeutic index should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.

Coadministration of known strong CYP2C19 inhibitors (e.g. fluconazole, fluoxetine, fluvoxamine and ticlopidine) should be avoided, and alternative drugs should be considered. If their use becomes necessary, then this should be done with caution, since they may increase lorlatinib plasma concentrations.

Coadministration of known strong CYP2C8 inhibitors (e.g. clopidogrel, gemfibrozil) should be avoided. If they must be used, then this should be done with caution, since they may increase lorlatinib plasma concentrations.

The results from *in vitro* studies showed that lorlatinib is a P-gp inhibitor. The concurrent use of drugs which are P-gp substrates with narrow therapeutic indices, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely needed during the study, caution should be exercised when coadministered P-gp substrates with narrow therapeutic indices with lorlatinib. Lorlatinib may increase the plasma concentrations of these drugs and patients should be closely monitored for safety and dose of the P-gp substrate with a narrow therapeutic index may need to be stopped or adjusted if necessary.

Any questions regarding the use of alternative medications should be directed to the sponsor for guidance.

### **8.5.2 Crizotinib**

The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of potent CYP3A inhibitors, including but not limited

to clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, telithromycin, troleandomycin, saquinavir, voriconazole, and grapefruit or grapefruit juice, **are not allowed in the study**. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

*In vitro* data indicate that the most pronounced inhibitory potential of crizotinib was observed toward CYP3A4 (testosterone)-mediated drug metabolism. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6. Crizotinib also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A. Caution (excluding those restricted medications mentioned above) must be exercised in patients receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A such as alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. In particular, coadministration of crizotinib with CYP3A4 substrates with narrow therapeutic indices including, but not limited to dihydroergotamine, ergotamine, pimozide, astemizole,\* cisapride,\* and terfenadine\* (\*withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation.

To protect patient safety, the following action should be exercised until more information is available:

Coadministration of strong CYP3A inhibitors (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]) is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely needed during the study, strong CYP3A inhibitors should be used with caution and patient closely monitored for safety. Caution should be exercised when coadministering drugs that are moderate CYP3A inhibitors (eg: aprepitant, cimetidine, ciprofloxacin, dronedarone, erythromycin, fluconazole, fluvoxamine, tofisopam, verapamil). Closely monitor the safety of patients and reduce the lorlatinib dose if necessary.

## **8.6 Contra-Indicated Medications**

Live vaccines are contraindicated whilst on study.

Lorlatinib and crizotinib are both simultaneous inhibitors and inducers of CYP3A4. Strong inducers and inhibitors of CYP3A4 can significantly decrease both lorlatinib, and crizotinib exposure, compromising efficacy.

Below is a list of contra-indicated medications. Also consult:

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>

**Known strong CYP3A inhibitors** (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

**Known strong CYP3A inducers** (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort).

**Known P-gp substrates** with a narrow therapeutic index (eg, digoxin).

Concurrent use of CYP3A substrates with narrow therapeutic indices (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozone, quinidine, sirolimus, tacrolimus within 12 days prior to the first dose of lorlatinib or crizotinib).

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy;
- Investigational agents other than lorlatinib;
- Radiation therapy (with the exception noted in the [Concomitant Radiotherapy 8.2p35](#));
- Other experimental pharmaceutical product;
- Herbal remedies with anticancer properties or known to potentially interfere with major organ function or study drug metabolism (e.g., hypericin)

## 8.7 Use with Caution

The following medications **should be avoided if possible** whilst participants are on study drug. If there are no alternatives, these drugs **may be continued/used with caution**:

The concurrent use of crizotinib with other bradycardic agents, medicinal products that are known to prolong the QT interval, and/or antiarrhythmics should be avoided. Close ECG monitoring will be provided.

A list of medicinal products that are known to prolong the QT interval can be found on under the new FDA classification:

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>

- **Summary of other medications to use with caution:** Any CYP450 inducers and inhibitors can affect crizotinib and lorlatinib exposure, leading to under-

dosing or over-dosing and should be used with caution, except those listed above as 'strong' above are excluded

- Warfarin/Coumadin: Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio
- Other bradycardic agents (e.g. beta blockers, verapamil, diltiazem, clonidine, digoxin etc.) due to increased risk of symptomatic bradycardia (e.g. syncope, dizziness, hypotension)
- H2 blockers (e.g. famotidine, ranitidine etc.) and Proton Pump Inhibitors (e.g. omeprazole, pantoprazole, rabeprazole etc.). Reduced efficacy of crizotinib and lorlatinib possible due to decreased absorption when gastric acid secretion suppressed (crizotinib requires acidic environment for absorption)

## **8.8 Prohibited**

Any other systemic anticancer therapy including, but not limited to: chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Hormonal contraception is allowed.

Use of any other investigational drug or device; medications that are known to be associated with the development of Torsades de Pointes. Medications that prolong the QT interval but are not known to be associated with Torsades de Pointes, should be avoided, but are not prohibited.

Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required). If a patient's clinical condition requires treatment with one of the prohibited classes of medications specified above, the clinical details of the situation should be discussed with the CIs and TMC at the earliest possible time to determine whether it is safe for the patient to continue treatment.

## **8.9 Concomitant Medication Reporting**

Concomitant medications will be recorded during the study, including medications used to treat serious adverse events or medications known to interact with the study medications. List any such medications.

## **8.10 Restrictions for Sexually Active Participants**

### **8.10.1 Females of Child-Bearing Potential**

Females of child-bearing potential should use reliable methods of contraception from the time of screening until 6 weeks after discontinuing study treatment. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (e.g. IUS Levonorgestrel Intra Uterine System (Mirena), medroxyprogesterone injections (Depo-Provera)), copper-banded intra-uterine devices and vasectomised partner. All

hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

### **8.10.2 Male Participants**

Male participants should be asked to use barrier contraceptives (i.e. by use of condoms) during sex with all partners during the trial and for a washout period of 4 months. Subjects should not father a child for 4 months after completion of study treatment. Subjects should refrain from donating sperm from the start of dosing until 4 months after discontinuing study treatment. If male subjects wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

### **8.11 Compliance**

Subject medication compliance will be determined at each clinic visit by tablet return count out of the sight of the patient and the patient counselled appropriately if significant non-compliance is determined.

The patient will be given a patient diary (Appendix 7.) to record any symptoms daily and confirm medication taken. This will be reviewed at each scheduled appointment.

## **9 STUDY TREATMENT DISCONTINUATION**

### **9.1 Subject Discontinuation**

Study treatment must be permanently discontinued for any of the following reasons:

- Disease progression by RECIST as determined by local investigator and radiology review unless the patient is considered to have ongoing clinical benefit by the investigator
- Unacceptable toxicity as determined by the patient or site investigator
- Need for treatment delay for more than 28 days (4 weeks) due to lack of toleration
- Global deterioration of health-related symptoms or death
- Required use of a concomitant treatment that is not permitted, as defined in section 8.6 and 8.8
- Confirmed diagnosis of interstitial lung disease (ILD)
- QTc prolongation with symptoms/signs of serious arrhythmia
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments
- Initiation of alternative anticancer therapy including another investigational agent
- Protocol non-compliance
- Pregnancy
- The occurrence of a psychiatric illness



- The patient declines further study treatment or withdraws their consent to participate in the study
- Patient lost to follow-up (data may still be collected from other sources, e.g., vital records, as allowed by local regulations)

Any patient who discontinues treatment will have this documented in the participant's medical record and eCRF. Participants who stop study treatment or wish to stop the study visits will be requested to continue follow-up visits according to the protocol or allow their ongoing health status to be periodically reviewed via phone contact or from their general practitioner or medical records.

## 9.2 Treatment beyond Progression

Patients may be considered for continuation of alternating treatment or treatment with continuous lorlatinib beyond radiographic progression per RECIST v1.1, and modified RECIST 1.1 for crizotinib (See section 4.3 and Figure 6.) at the discretion of the investigator and after appropriate discussion with the patient and if the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression of critical anatomical site (i.e. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- New CNS disease may be managed with focal therapy e.g. stereotactic radiosurgery (SRS) as per standard of care OR if on crizotinib, can change to continuous lorlatinib at TMC discretion
- The decision to defer alternative treatment options in favor of continuing study treatment at the time of initial progression is documented in the patient's medical record, and in the Trial Master File as a "Note To File"

## 9.3 Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioural reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events. If a patient does not return for a scheduled visit, every effort should be made to contact the patient and all efforts documented.

If the patient also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

#### **9.4 Post-Study Treatment**

Treatment after discontinuation of study treatment is at the discretion of the site-specific primary investigator. If the patient is still benefiting from study treatment at the end of the study, ongoing supply will be provided by the manufacturer until the product is available to the public. Please refer to section 9.2 above.

## 10 ASSESSMENT PLAN

### 10.1 Schedule of Assessments

	Screening	Induction Phase	Alternating phase							End of alternating treatment		End of Treatment and Follow Up		
	Within 14 days of starting study treatment	Cycle 1 Day 1, Day 15 and Weeks 5 and 9 Lorlatinib	Cycle 2a Crizotinib	Cycle 2b Week 1 and 5 Lorlatinib	Cycle 3a Crizotinib	Cycle 3b Week 1 and 5 Lorlatinib	Cycle 4a Crizotinib	Cycle 4b Week 1 and 5 Lorlatinib	Cycle ≥ 5 Crizotinib alternating with lorlatinib	PFS1+	Until progression (if treated beyond PFS 1+)	End of Treatment Visit	30 Day Follow Up	Survival Follow Up
		On study treatment – each cycle is 12 weeks, with 4 weekly study visits (±3 days)							4 weekly study visits (±3 days)			30 days post last dose (±3 days)	Every 12 weeks ± 7 days	
Informed Consent	X													
Medical History	X													
Clinical Assessment with ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X		
Routine Fasting Bloods (Haematology & Biochemistry) <sup>1</sup>	X	X	X	X	X	X	X	X	X	X	X	X		
Bloods for Hepatitis B, C and HIV	X													
Pregnancy Test (WOCBP only) <sup>2</sup>	X	As clinically indicated												
Urinalysis <sup>3</sup>	X	As clinically indicated												
12 lead ECG	X		X	X	X	X	X		Every 12 weeks		X	X		

Cognitive Assessment (MiniCog)	X		X	X	X				X (as clinically indicated)	X	X	X		
PRO and Mood Assessment		X (Weeks 1 and 9)		X		X (Week 9)	X		Every 12 weeks	X	X	X		
Tumour Imaging <sup>4</sup>	X		X	X	X	X	X		Every 12 weeks <sup>5</sup>	X	X <sup>5</sup>	X		
Translational Research bloods <sup>6</sup>	X		X	X	X	X (Week 1)		X (Week 1)	X <sup>6</sup>	X	X	X <sup>7</sup>		
Pharmacokinetics (PK) bloods <sup>7</sup>			X	X										
Biopsy or pleural sample for research	X <sup>8</sup>									X <sup>9</sup>		X <sup>9</sup>		
Confirmed ALK translocation	X									X		X		
Survival and anti-cancer treatment										X		X		X <sup>10</sup>

#### Footnotes

- Haematology tests must include a full blood count and differentials. Biochemistry tests must include the following: glucose, urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein and albumin. Fasting blood glucose, total cholesterol and triglycerides. Other blood tests may be performed as clinically indicated.
- Serum or urine BHCG for women of child-bearing potential must be tested
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick permitted as clinically indicated
- CT Chest, Abdomen and Pelvis and MRI Brain. Tumour assessments will take place with each drug switch until the end of Cycle 3 and then at the end of each cycle/12 weekly prior to restarting crizotinib if remaining on alternating therapy. In the event of a treatment delay/dose interruption, restaging imaging can be delayed by up to two weeks from the scheduled timepoint and must be approved by the TMC. When the patient is deemed appropriate to resume treatment the dates of the cycles will remain as scheduled and will not be delayed ee.g. if a dose interruption occurs on day 22 of a crizotinib cycle and the patient is able to resume therapy on day 8 of the following cycle the patient will resume treatment with lorlatinib from day 8 and continue. Imaging reporting will not be centrally reviewed and recorded based on the formal RECIST 1.1 reporting by the local radiologist, verified by the study investigator. If a patient is being 'treated beyond progression' complete staging imaging should occur at least every 12 weeks, earlier at the discretion of the Investigator based on safety and best practice.
- Tumour Imaging should be completed every 12 weeks from Cycle 4 onwards, unless clinically indicated for more frequent monitoring at PI/Sub-I discretion particularly in those being treated beyond progression.
- Next generation sequencing (NGS) and Proteomics bloods will be collected Cycles 2a, 2b, 3a, 3b, every 12 weeks thereafter and at disease progression. Translational research bloods should be collected at each PFS time point also and prior to the start of new anti-cancer therapies, where possible. Please refer to the Laboratory Manual for full collection, processing and storage details.
- Pharmacokinetics (PK) bloods will be collected at Cycle 2a and Cycle 2b drug switch visits, at +1, +2, +4, +6 and +24 hours post dose. Please refer to the Laboratory Manual for full collection, processing and storage details.
- Pre-trial biopsy or pleural sample should be obtained (if clinically safe) to confirm ALK translocation for trial eligibility
- End of trial biopsy or pleural fluid sample should be obtained (if clinically safe) prior to the initiation of new anti-cancer therapy
- Contact by phone is acceptable for ongoing survival data collection after trial withdrawal or discontinuation

## **10.2 Re-challenge**

If patients experience a suspected drug related adverse event, they can interrupt the study medication until the symptoms resolve and then can reintroduce the study medication at same/reduced dose (depending on AE). If the reaction reappears at G2-3 then the study medication can be withheld and if recovers reduced one further level. If the AE recurs in the first episode as G4 or recurs after two dose reductions, the study medication should be discontinued after consultation with the TMC.

## **11 ASSESSMENT PHASE DEFINITIONS AND SPECIAL CIRCUMSTANCES**

### **11.1 Screening/Baseline**

All screening procedures must be performed within 14 days prior to enrollment, unless otherwise specified. If screening procedures cannot be completed within 14 days of consent, they may re-sign the consent form to extend the screening period for an additional 14 days.

### **11.2 On Treatment**

Assessments during treatment may be performed 3 days prior or after the specified time point.

### **11.3 End of Treatment**

All end of treatment assessments must be performed within 30 days after the end of study treatment.

### **11.4 30-day Safety Assessment**

A safety assessment should be performed to include any adverse events occurring within 30 days after the last dose of study treatment.

### **11.5 Follow-Up After Treatment**

Subjects who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, state-based cancer registries and/or the national mortality registry (AIHW).

Patients will be contacted by phone every 12 weeks after the study treatment ceases to enquire about subsequent anti-cancer therapies and survival status.

## 11.6 After Study is Closed

The study will be closed after it is deemed sufficient data required for objectives has been collected and analysed. This is predicted to occur 18 months after the last patient is enrolled to the trial.

The pharmaceutical company has agreed to continue to provide the medications free of charge to the patient whilst still responding after the study closes.

## 11.7 Special Circumstances

In the case of special circumstance where it may be unsafe for the patient to attend clinic visit or complete scheduled study assessments, it is at the Principal Investigator's discretion which study assessments can be altered and which assessments are omitted to ensure patient and staff safety, ie telehealth consultations in lieu of physical examinations and adverse events review. PI and site staff including Trial Pharmacy may also allow for medications to be posted with temperature monitoring (where available) and tracking, in line with local site policy.

## 12 SAFETY REPORTING

### 12.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below). Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test)
- Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device

All adverse events, which occur from the start of study treatment until 30 days after the end of study intervention, must be reported.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (i.e. the subject is at risk of death at the time of the event)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

#### NOTES:

The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events which may not be immediately life-threatening or result in death or hospitalisation but which may jeopardise the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Patient Information Sheet and Informed Consent Form or elsewhere in the protocol.

An event is causally related if there is a reasonable possibility that the drug caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

## 12.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the TMC and Pfizer, who are providing the study medication within 1 working day of the investigator becoming aware of the event. SAEs must be reported from the start of treatment, up to 30 days from the end of study intervention.

For all SAEs, the following forms need to be completed and faxed to the Pfizer Adverse Event Reporting at 1800 034 314 (Australia only) or +1 973 660 8913

- Pfizer Reportable Event Fax Cover Sheet
- Pfizer Investigator Initiated Research or Clinical Research Collaboration
- Interventional Study Serious Adverse Event Report Form
- Pfizer Vaccine Supplemental Form (if applicable)
- Pfizer Exposure during Pregnancy (EDP) Supplemental Form (if applicable)

Northern Sydney Local Health District Human Research Ethics Committee (NSLHD HREC) have adopted the NHMRC Safety Reporting Guidelines, in addition to existing NSW Health guidelines. NSLHD HREC only require significant safety issues

(a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial) and annual safety reports to be reported. SUSARS will only be reported to the Research Governance Office at the site at which it occurred, unless it was a significant safety issue, where HREC must be notified.

The TMC Project Manager will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The TMC, Project Manager will be responsible for providing reports to the Lead HREC.

The study sponsor will submit 'reportable safety events' to the TGA in Australia and to the lead centre to provide to the regulatory authorities in the other participating country for which the sponsor is responsible.

The following information will be recorded for each Serious Adverse Event:

- Event description including classification according to CTCAE v 4.3
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity / Worst Grade
- Attribution to study intervention (specify investigational agent or treatment package)
- Expectedness (listed in IB/product information, specify as above)
- Action taken with study intervention (specify investigational agent or treatment package), including re-challenge (if done)
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE including end date if recovered

### **12.3 Pregnancy**

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The sponsor site must be notified within 1 working day using the SAE form and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the investigator and the TMC collectively. The partner should be counselled and followed as described above.



## **13 CENTRAL REVIEW AND SPECIMEN COLLECTION**

### **13.1 Central Tissue Collection**

Paraffin-embedded tissue blocks will be collected for central histology review (mandatory for eligibility), and consent will be sought for translational tissue study. Handling of biospecimens and contact details etc of labs and couriers will be as per standard laboratory procedures and practice.

### **13.2 Central Blood Collection**

This blood collection is required for all study patients. Serum and plasma for biomarkers will be collected and initially processed at each site. The frozen samples will be sent to a central lab for analysis. Collection and processing procedures are outlined in the Study Laboratory Manual.

### **13.3 Central Review**

Imaging and archival biopsy samples will not be reviewed centrally. Tissue and blood samples for translational outcomes will be stored and analysed centrally at the sponsor site affiliated laboratory, The Bill Walsh Translational Cancer Research Laboratory of the Kolling Institute.

## **14 TREATMENT INFORMATION**

### **14.1 Investigational Product(s) Name (drugs are not approved, or being used outside of an approved indication)**

Lorlatinib is not yet TGA approved as of October 2019. Preliminary early phase and clinical data has shown great efficacy and tolerability as well as anti-tumour potency.

Crizotinib is approved for *ALK* mutated lung cancer in Australia, however fixed alternative dosing is an off-label use.

### **14.2 Description of Investigational Product**

The recommended storage condition for crizotinib and lorlatinib is room temperature. Do not refrigerate or freeze. Capsules should be swallowed whole with a glass of water. Medication should be taken with food. Patients should not have grapefruit juice while on either study drug.

### **14.3 Supply of Investigational Product**

Pfizer will be responsible for the delivery of drug to the lead site.

All used bottles of study drug must be returned to the study sponsor or destroyed in an appropriate manner according to the standard practice at each study centre.

Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

#### **14.4 Drug Accountability**

The Pharmacy Department at participating institutions will maintain a record of drugs dispensed for each patient and subsequent returns (if oral). The Pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Patients will be asked to return unused drug and empty drug containers at each return visit.

### **15 STATISTICAL CONSIDERATIONS AND FEASIBILITY**

Feasibility will be based on the successful demonstration that patient disease can be controlled after completion of at least one 12 week sequence of alternating lorlatinib/crizotinib in at least 12 patients (24 weeks total of treatment). Patients who continue on alternating therapy 'beyond progression' are considered as also maintaining disease control and may be included in this feasibility assessment. Historical data from the PII lorlatinib trial will be used to benchmark the survival endpoints (PFS: 5.5-6.9 months, differing for number of prior lines of therapy) (2).

A minimum sample size of 25 is expected to be required in order to have 20 eligible participants to enter the active alternating drug schedule. Accrual of 25 patients over an 18-month period is deemed feasible based on high recruitment of Australian patients in previous *ALK* drug trials. Given the Covid-19 pandemic, additional funding has been provided to extend the recruitment period for an additional 6 months, for a total of 24 months for recruitment. Strong collegiate tertiary referral for trials in rare lung tumour subgroups has been documented, particularly in the setting of refractory disease (39). Furthermore, there are **no ALKi's currently available** for those patients having received 2 lines of ALKi therapy and there are currently no registered competing trials in this patient population in Australasia.

#### **15.1 Sample Size**

Approximately 25 patients will be enrolled to enable at least 20 patients complete one cycle of alternating therapy.

#### **15.2 Statistical Analysis**

A total sample size of 25 participants are anticipated to be required, accounting for early drop off, to enable at least 20 patients to enter the alternating 'active' phase of the clinical trial. Only patients in the alternating phase will be included in the primary outcome analysis. Results from patients treated with continuous lorlatinib only will be reported separately via the secondary outcomes.

TTTF as the primary outcome measure will start from the initiation of alternating therapy i.e. after 12 weeks of induction lorlatinib and will be presented in the context of this induction period. Patients who continue alternating therapy as 'treatment

beyond progression' will be included in this primary analysis with the end point for all patients included to be when alternating therapy ceases.

The sample size has been chosen based on a scientific estimate of the number of patients required to capture a representative cohort in a rare tumour including those with CNS disease and to enable a signal to carry forward further investigation in an expanded cohort.

Descriptive statistics will be used to report ORR and safety. The Kaplan Meier Method will be used to report PFS and OS.

### 15.3 Interim Analyses

The Trial Management Committee (TMC) will consist of the Clinical Leads (A/Prof N Pavlakis/Dr Itchins) and Project Manager at the lead site Royal North Shore Hospital and Prof B Solomon from the PMCC. The TMC will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

The TMC will convene at an agreed time for a teleconference to review the trial progress and updates. Timing of TMC reviews will be triggered by unexpected SAEs or SUSARS, analysis of progress through the study protocol of the first 12 patients after 12 weeks, then quarterly.

Suspending or stopping recruitment will be considered if:

- Clinically significant adverse events thought to be related to study treatment are unexpectedly frequent or severe (include specific events and rates, if known)
- Medical or ethical reasons emerge affecting continued performance of the study
- Accrual is too slow
- If of the first 10 patients who enter the alternating active phase of the trial,  $\geq 8$  i.e. at least 3 patients remain on alternating therapy (30%) not having reached a TTF event. Between the accrual of the 10<sup>th</sup> patient, and the conduct of the interim analysis by the MTC, patients can continue to be enrolled to the study; accrual will not halt.

Analysis	Criteria for Conduct of Analysis
Interim Analysis 1: Safety and efficacy signal to proceed with trial recruitment	To be performed after the first 10 patients have completed one alternating cycle. *Study deemed worthy to continue provided at least 30% remain on alternating therapy (+24 weeks on trial) i.e. the treatment has not failed (from any cause) in $\geq 3/10$ patients

Final Analysis 1: Interim TTTF and interim PFS1 and non-primary outcomes	To be performed 6 months after last patient enrolled, or when 70% have achieved a TTTF event, whichever occurs first
Final Analysis 2: Final TTTF and non-primary outcomes	To be performed 12 months after the last patient enrolled, or when 100% have achieved a TTTF failure event, whichever occurs first
Additional Final Analyses	At the discretion of the TMC

## 15.4 Independent Safety and Data Monitoring Committee

This study does not have an ISDMC. The lead clinical trial site team, Royal North Shore Hospital, will be the responsible site for ensuring safety procedures are adhered to and will undertake regular data monitoring.

## 15.5 Outcome Assessment Committee

There is no outcome assessment committee for this trial. The TMC will be responsible for following Standard Operating Procedures 'SOP', defined by the standard practices and daily processes conducted to assure execution of research tasks in accordance with institutional, state and federal requirements.

## 16 ADMINISTRATIVE ASPECTS

### 16.1 Ethics and Regulatory Compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the TMC, principal investigator and HREC must be advised immediately.

### 16.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Royal North Shore Cancer Centre Clinical (RNSCC)

Trials Department and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

Personal data identifying trial subjects will be held securely at each primary site for the purpose of follow up if the patient is unable to/wishes to discontinue clinic-based follow-up. The vital status of the subject (alive or dead) will be followed up through the Australian Institute of Health and Welfare (AIHW) National Death Index (NDI), cancer morbidity data through the state-based cancer registries and/or updated contact details from the Health Insurance Commission (HIC). NDI, HIC and cancer registry approvals will be obtained. All coded trial data will be stored securely at RNSCC as the central site.

### **16.3 Protocol Amendments**

Changes and amendments to the protocol can only be made by the TMC. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

### **16.4 Data Handling and Record Keeping**

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs. All required data entry fields must be completed. The investigator will confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

- Subject's name, contact information and protocol identification
- The date that the subject entered the study, and subject number
- A statement that informed consent was obtained (including the date)
- Relevant medical history
- Dates of all subject visits and results of key trial parameters.
- Occurrence and status of any adverse events
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation

All study-related documentation will be maintained for 15 years following completion of the study.

## **16.5 Study Monitoring**

Data from this study will be monitored by RNSCC clinical trials staff and the TMC. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator's site file and drug handling records. The sponsor will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorised clinical trial staff at each site direct access to their medical records and the study data.

## **16.6 Audit and Inspection**

This study may be subject to audit or inspection by representatives of the TMC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration (TGA), HREC).

## **16.7 Clinical Study Report**

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the HREC and relevant site governance officers, as well as participants (on request).

## **16.8 Publication Policy**

The Trial Management Committee will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets in individual names based on contribution. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. All publications must receive prior written approval from the TMC prior to submission.

## **16.9 Insurance, Indemnity and Funding**

Each study site will act as its own Sponsor for the purposes of insurance and indemnity.

Pfizer is supplying the study drugs and has contributed a \$387,566 grant towards the running of the study, however it has no control over the study design or data generated from the study. The investigator's and their sites retain rights to intellectual property generated by the study. This is detailed in a separate funding agreement negotiated between NSLHD and Pfizer.

A \$100,000 *Fight for A Cure* grant has been awarded to carry out the translational work of the trial provided by the philanthropic group Fight for a Cure.

The results from this trial are planned to be published by the trial working group without restriction to positive findings.

## 17 APPENDICES

### Appendix 1. Abbreviations

ALKi	Anaplastic Lymphoma Kinase Rearranged Non-Small Cell Lung Cancer Inhibitor (Tyrosine Kinase Inhibitor)
<i>ALK</i>	Anaplastic Lymphoma Kinase Gene Rearranged Non-Small Cell Lung Cancer
<i>ALK+</i>	ALK Gene Rearrangement Positive Patient
ATP	Adenosine Triphosphate
BAL	Bronchoalveolar lavage
BID	Twice Daily
BNP	B-type natriuretic peptide
CHF	Congestive Heart Failure
CI	Chief Investigator
CNS	Central Nervous System
CT	Computed Tomography
ct	Circulating Tumour (DNA)
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DNA	Deoxynucleic Acid
ECG	Echocardiogram
ECOG	European Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medical Association
EML	Echinoderm microtubule-associated protein-like 4
FACT-L	Functional Assessment of Cancer- Lung
HIV	Human Immunodeficiency Virus
HREC	Human Research and Ethics Committee
IHC	Immunohistochemistry
KD	Kinase Domain
KRAS	Kirsten RAt Sarcoma virus
mg	Milligram
Mo	months
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute, Bethesda, Maryland, USA
NGS	Next Generation Sequencing



NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
P	Phase (Of Trial)
PFS	Progression Free Survival
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PST	Potential Sight Threatening
QD	Once Daily
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribo deoxynucleic Acid
SAE	Serious Adverse Event
SBRT	Stereotactic Beam Radiotherapy
SDMC	Safety and Data Monitoring Committee
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reaction
SVL	Severe Vision Loss
TDS	Three times daily
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase Inhibitor
TMC	Trial Management Committee
TNA	Tumour Nucleic Acid
ULN	Upper Limit of Normal
US FDA	United States Food and Drug Administration
v	version
WOCBP	Women of Child Bearing Potential

## Appendix 2. RECIST v 1.1

### Response Evaluation Criteria in Solid Tumours (RECIST v1.1)

These instructions are based on the guidelines recommended in 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)

#### Evaluable for response

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

#### Disease and lesion definitions

##### Measurable Disease

Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as

- $\geq 20$  mm with chest x-ray
- $\geq 10$  mm with CT scan or clinical examination.
- Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component  $\geq 10$  mm by CT scan).

*Malignant lymph nodes* must be  $\geq 15$ mm in the short axis to be considered measurable; only the short axis will be measured and followed.

All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

##### Non-measurable Disease

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

##### Target Lesions

When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs,

but in addition should be those that lend themselves to *reproducible repeated measurements*.

Note that pathological lymph nodes must meet the criterion of having a short axis of  $\geq 15$  mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis  $\geq 10$  mm but  $<15$  mm) should be considered non-target lesions. Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be use

#### Patients with measurable disease at baseline

Target lesions	Non-target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD/ not all evaluated	No	PR
SD	Non-PD/ not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

#### Patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

### Appendix 3. Functional Assessment of Cancer- Lung (FACT-L)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

#### PHYSICAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit
GP1	I have a lack of energy.....	0	1	2	3
GP2	I have nausea.....	0	1	2	3
GP3	Because of my physical condition, I have trouble meeting the needs of myfamily.....	0	1	2	3
GP4	I have pain.....	0	1	2	3
GP5	I am bothered by side effects of treatment.....	0	1	2	3
GP6	I feel ill.....	0	1	2	3
GP7	I am forced to spend time in bed.....	0	1	2	3

#### SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit
GS1	I feel close to my friends.....	0	1	2	3
GS2	I get emotional support from my family.....	0	1	2	3
GS3	I get support from my friends.....	0	1	2	3
GS4	My family has accepted my illness.....	0	1	2	3
GS5	I am satisfied with family communication about my illness.....	0	1	2	3

GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.</i>				
GS7	I am satisfied with my sex life.....	0	1	2	3

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

**EMOTIONAL WELL-BEING**

		Not at all	A little bit	Some-what	Quite a bit
GE1	I feel sad.....	0	1	2	3
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3
GE3	I am losing hope in the fight against my illness.....	0	1	2	3
GE4	I feel nervous.....	0	1	2	3
GE5	I worry about dying.....	0	1	2	3
GE6	I worry that my condition will get worse.....	0	1	2	3

**FUNCTIONAL WELL-BEING**

		Not at all	A little bit	Some-what	Quite a bit
GF1	I am able to work (include work at home).....	0	1	2	3

GF2	My work (include work at home) is fulfilling.....	0	1	2	3
GF3	I am able to enjoy life.....	0	1	2	3
GF4	I have accepted my illness.....	0	1	2	3
GF5	I am sleeping well.....	0	1	2	3
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3
GF7	I am content with the quality of my life right now.....	0	1	2	3

**ADDITIONAL CONCERNS**

		Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath.....	0	1	2	3	4
C2	I am losing weight.....	0	1	2	3	4
L1	My thinking is clear.....	0	1	2	3	4
L2	I have been coughing.....	0	1	2	3	4
B5	I am bothered by hair loss.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
L3	I feel tightness in my chest.....	0	1	2	3	4
L4	Breathing is easy for me.....	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking.....	0	1	2	3	4

#### **Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE)**

Adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed below.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address:

[http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

## Appendix 5. Medications with Potential PR Interval Prolongation Effect

Note that the drugs listed below are examples and this is not intended to be an all-inclusive listing (from Nada A, et al. Am Heart J 2013;165:489-500)

<b>Electrophysiologic Effects of Select Drugs on PR Interval Based on Product Labeling</b>		
<b>Drug</b>	<b>Action</b>	<b>Indications</b>
Affecting AV nodal conduction (PR interval)		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyramide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		
Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT3 receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial
<p>Drugs were initially screened using the PDR3D database for PR interval prolongation using terms "PR interval prolongation", "AV block", "AV conduction delay", or "heart block". Drugs were subsequently selected for inclusion on the basis on descriptions of PR interval prolongation/AVB contained with Warning or Precautions sections of drug labels. PSVT, Paroxysmal supraventricular tachycardia.</p>		



## Appendix 6. Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
  - 0 I do not feel sad.
  - 1 I feel sad
  - 2 I am sad all the time and I can't snap out of it.
  - 3 I am so sad and unhappy that I can't stand it.
2.
  - 0 I am not particularly discouraged about the future.
  - 1 I feel discouraged about the future.
  - 2 I feel I have nothing to look forward to.
  - 3 I feel the future is hopeless and that things cannot improve.
3.
  - 0 I do not feel like a failure.
  - 1 I feel I have failed more than the average person.
  - 2 As I look back on my life, all I can see is a lot of failures.
  - 3 I feel I am a complete failure as a person.
4.
  - 0 I get as much satisfaction out of things as I used to.
  - 1 I don't enjoy things the way I used to.
  - 2 I don't get real satisfaction out of anything anymore.
  - 3 I am dissatisfied or bored with everything.
5.
  - 0 I don't feel particularly guilty
  - 1 I feel guilty a good part of the time.
  - 2 I feel quite guilty most of the time.
  - 3 I feel guilty all of the time.
6.
  - 0 I don't feel I am being punished.
  - 1 I feel I may be punished.
  - 2 I expect to be punished.
  - 3 I feel I am being punished.
7.
  - 0 I don't feel disappointed in myself.
  - 1 I am disappointed in myself.
  - 2 I am disgusted with myself.
  - 3 I hate myself.
8.
  - 0 I don't feel I am any worse than anybody else.
  - 1 I am critical of myself for my weaknesses or mistakes.
  - 2 I blame myself all the time for my faults.
  - 3 I blame myself for everything bad that happens.
9.
  - 0 I don't have any thoughts of killing myself.
  - 1 I have thoughts of killing myself, but I would not carry them out.
  - 2 I would like to kill myself.
  - 3 I would kill myself if I had the chance.
- 10.

- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

- 0 I am no more irritated by things than I ever was.
- 1 I am slightly more irritated now than usual.
- 2 I am quite annoyed or irritated a good deal of the time.
- 3 I feel irritated all the time.

12.

- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13.

- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.

- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
- 3 I believe that I look ugly.

15.

- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
- 2 I have to push myself very hard to do anything.
- 3 I can't do any work at all.

16.

- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
- 2 I get tired from doing almost anything.
- 3 I am too tired to do anything.

18.

- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

19.

- 0 I haven't lost much weight, if any, lately.
- 1 I have lost more than five pounds.
- 2 I have lost more than ten pounds.

- 3 I have lost more than fifteen pounds.
- 20.
- 0 I am no more worried about my health than usual.
- 1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
- 2 I am very worried about physical problems and it's hard to think of much else.
- 3 I am so worried about my physical problems that I cannot think of anything else.
- 21.
- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I have almost no interest in sex.
- 3 I have lost interest in sex completely.

### INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score \_\_\_\_\_ Levels of Depression

Raw Scores	Depression Severity
0-13	Indicates minimal depression
14-19	Indicates mild depression
20-28	Indicates moderate depression
29-63	Indicates severe depression

<https://www.nctsn.org/measures/beck-depression-inventory-second-edition>  
 Accessed 14/2/2019

## Appendix 7. Patient Diary Card (to be issued each visit)

### ALKternate Clinical Trial

Patient Name & Number

Cycle Number

Insert Site Logo

Day	Date	Lorlatinib taken	Side Effects Experienced
1		<input type="checkbox"/> Morning	
2		<input type="checkbox"/> Morning	
3		<input type="checkbox"/> Morning	
4		<input type="checkbox"/> Morning	
5		<input type="checkbox"/> Morning	
6		<input type="checkbox"/> Morning	
7		<input type="checkbox"/> Morning	
8		<input type="checkbox"/> Morning	
9		<input type="checkbox"/> Morning	
10		<input type="checkbox"/> Morning	
11		<input type="checkbox"/> Morning	
12		<input type="checkbox"/> Morning	
13		<input type="checkbox"/> Morning	
14		<input type="checkbox"/> Morning	
15		<input type="checkbox"/> Morning	

### ALKternate Clinical Trial

Patient Name & Number

Cycle Number

Insert Site Logo

Day	Date	Lorlatinib taken	Side Effects Experienced
16		<input type="checkbox"/> Morning	
17		<input type="checkbox"/> Morning	
18		<input type="checkbox"/> Morning	
19		<input type="checkbox"/> Morning	
20		<input type="checkbox"/> Morning	
21		<input type="checkbox"/> Morning	
22		<input type="checkbox"/> Morning	
23		<input type="checkbox"/> Morning	
24		<input type="checkbox"/> Morning	
25		<input type="checkbox"/> Morning	
26		<input type="checkbox"/> Morning	
27		<input type="checkbox"/> Morning	
28		<input type="checkbox"/> Morning	
29		<input type="checkbox"/> Morning	
30		<input type="checkbox"/> Morning	

Next Appointment: \_\_\_\_\_

**ALKternate Clinical Trial**

Patient Name &amp; Number

Cycle Number

Insert Site Logo

Day	Date	Crizotinib taken		Side Effects Experienced
1		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
2		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
3		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
4		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
5		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
6		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
7		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
8		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
9		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
10		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
11		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
12		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
13		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
14		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
15		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	

**ALKternate Clinical Trial**

Patient Name &amp; Number

Cycle Number

Insert Site Logo

Day	Date	Crizotinib taken		Side Effects Experienced
16		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
17		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
18		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
19		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
20		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
21		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
22		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
23		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
24		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
25		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
26		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
27		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
28		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
29		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	
30		<input type="checkbox"/> Morning	<input type="checkbox"/> Evening	

Next Appointment: \_\_\_\_\_

## Appendix 8. Cognitive Assessment – MiniCog

**Mini-Cog®**

### Instructions for Administration & Scoring

ID: \_\_\_\_\_ Date: \_\_\_\_\_

#### Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.<sup>1-9</sup> For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

#### Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

#### Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Word List Version: \_\_\_\_\_ Person's Answers: \_\_\_\_\_

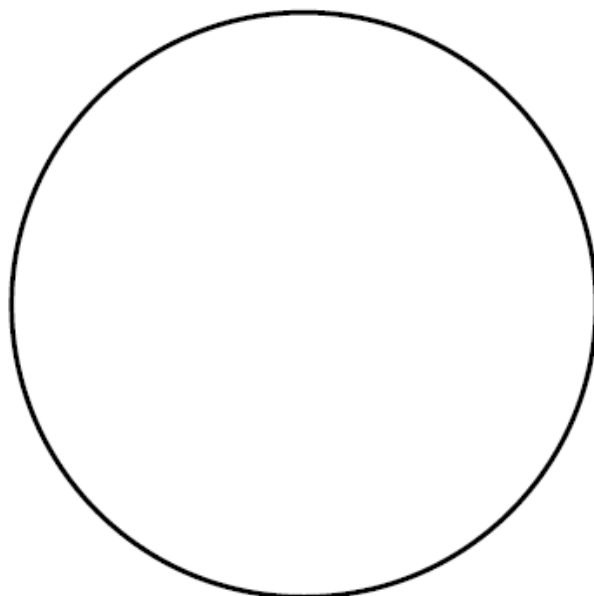
#### Scoring

Word Recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
Total Score: _____ (0-5 points)	Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

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v. 01.19.16

## Clock Drawing

ID: \_\_\_\_\_ Date: \_\_\_\_\_



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