Trial Title: FAST study: Feasibility ASessment of circulating Tumour DNA (ctDNA) in the diagnosis of advanced lung cancer in patients

Internal Reference Number / Short title: FAST study

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No potential conflicts of interest declared

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Health Disability Ethics Committee and Regulatory Authorities unless authorised to do so.

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1. KEY TRIAL CONTACTS

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Funder(s)	Health Research Council New Zealand University of Otago Deans Research Grant New Zealand Society of Oncology

2. LAY SUMMARY

Lung cancer is the leading cause of cancer related death and disproportionately disadvantages Māori both in incidence and mortality rates. In New Zealand, pathological diagnosis and staging can take months after initial symptoms with frequent first-presentations to emergency services. The diagnosis is reliant on specialist histological examination of tumoural tissue obtained by invasive biopsy, and subsequently tested for oncogenic mutations. Molecular testing for oncogenic mutations in lung cancer is crucial as oncogene driven lung cancers have highly effective treatments that prolong survival from months to years, and are much better tolerated than traditional chemotherapy. Our study aims to develop a blood-based diagnostic test using circulating tumour DNA (ctDNA) to rapidly identify oncogenic mutations so that patients can be started on appropriate, effective treatment sooner.

This study will recruit forty-five patients with suspected metastatic lung cancer from Te Whatu Ora Capital, Coast and Hutt Valley as well as Te Whatu Ora Te Toka Tumai Auckland. Patients who are unable to obtain a standard diagnostic biopsy or if there is insufficient tissue for molecular analysis are eligible for the study. Patients will undergo a blood test (40mL of blood) and a questionnaire about the acceptability of this testing process. The blood will be analysed using next generation sequencing (NGS) to study a panel of genes that may be mutated in lung cancer to the selection of treatments. Clinically relevant results from the genomic testing will be fed back to the treating clinician.

3. SYNOPSIS

Trial Title	FAST study: Feasibility ASsessment of circulating Tumour DNA (ctDNA) in the diagnosis of advanced lung cancer in patients	
Internal ref. no. (or short title)	FAST study	
Funder	Health Research Council New Zealand Deans Research Grant, University of Otago New Zealand Society of Oncology	
Clinical Phase	Single arm phase II	
Trial Design	Prospective feasibility study	
Trial Participants	Inclusion: 1. Radiological advanced lung cancer (AJCC 8th edition TNM M1a, M1b or M1c) - Radiologist confirmed suspicion of malignancy on CXR or CT and clinician opinion likely lung cancer primary 2. Unable to pursue molecular testing of a histological sample - Due to anatomical location/risk of complications - Due to patient preference - Insufficient tissue for molecular testing 3. Not suitable for cytotoxic chemotherapy but fit for molecularly targeted treatment, due to patient comorbidity, performance status or patient preference 4. Life expectancy expected more than 4 weeks 5. Patient unable to have single agent immunotherapy Exclusion: 1. Performance status ECOG 4	
Sample Size	40-50	
Planned Trial Period	2.5 years (May 2023-Dec 2025)	
Planned Recruitment period	2 years	
Planned Recruitment period	May 2023-May 2025	
	Objectives	Outcome Measures
Primary	To assess the feasibility of ctDNA to identify actionable mutations in patients with suspected advanced lung cancer	1) Recruitment rate over study period (12 months) 2) Proportion of patients with reportable ctDNA samples

Secondary	1) To identify the turnaround time for ctDNA test as a diagnostic procedure for advanced lung cancer 2) To assess patients' acceptability of the ctDNA test and impact on patient care planning 3) To assess clinicians' acceptance of the use of ctDNA as a diagnostic process 4) Survival at 3 months	1) Turnaround time from time of blood test collection to result being fed back to clinician 2) Patients' response to ctDNA acceptability questionnaire 3) Clinicians' response to ctDNA acceptability questionnaire – two parts, one on the impact on the logistics/therapeutic relationship at the time of diagnostic work up; second part at the time of results being fed back 4) Non-contact assessment of survival at 3 months from enrolment into study
Intervention(s) • IMP(s) • Other intervention(s)	Blood test	

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
ctDNA	Circulating tumour deoxyribonucleic acid
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice

GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NGS	Next Generation Sequencing
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Lung cancer is New Zealand's top cancer research priority as it is the leading cause of cancer-related death, and kills 1600 New Zealanders each year [1]. Importantly, lung cancer is an urgent equity issue as it is the largest cause of cancer outcome disparities between Māori and non-Māori, with incidence and mortality being three to four times higher in Māori compared to non-Māori [1]. Most patients present with advanced disease where treatments are no longer curative [2]. Again, Māori and Pasifika patients are more likely to present with more advanced disease and are particularly disadvantaged due to poor access to healthcare [3].

In advanced disease, an invasive biopsy is required to diagnose the cancer subtype and identify the presence of an actionable mutation in order to determine a treatment pathway. Frequently, after initial histological examination there is insufficient remaining tissue to undertake further molecular analysis. Concerningly, approximately 15-20% of patients with advanced lung cancer do not have a histological

diagnosis, potentially indicating a significant proportion of patients are missing out on life-prolonging treatment as a result [2]. Additionally, some patients are too unwell to tolerate invasive diagnostic biopsies.

Traditionally, cytotoxic chemotherapy has been the mainstay of treatment for advanced lung cancer, improving the prognosis by short months (add ref). More recently, immunotherapy as monotherapy or in combination with chemotherapy has improved the survival further [4-6]. However, the benefit of immunotherapy is generally not observed in patients with oncogenic mutations [7]. Furthermore, patients who are frail (defined as having poor performance status) are unlikely to benefit from treatments other than molecularly targeted therapy [8-10]. Molecularly targeted therapy has a significantly higher response rate than chemotherapy, benefiting approximately 80% of treated patients and improves the average survival from months to years [11-14]. A response in the cancer to targeted therapy often occurs earlier than when receiving chemotherapy and rapid identification of actionable mutations in this patient population is greatly needed.

Currently, the American National Comprehensive Cancer Network (NCCN) guidelines recommend molecular testing to identify actionable mutations in nine genes, namely *EGFR, ALK, BRAF, KRAS, MET, NTRK1/2/3, RET, ROS1,* and *ERBB2* [15]. Of these nine actionable genes, only treatments that target *EGFR* and *ALK* have publicly funding in New Zealand [15]. Based on tissue genotyping of non-squamous, non-small cell lung cancers, an actionable *EGFR* mutation is detected in approximately 20% and *ALK* rearrangement is detected in 3-5% of patients. A recent New Zealand study found that the population risk of *EGFR* mutated lung cancer was significantly higher in Māori, Pasifika and Asian patients compared to New Zealand Europeans [16]. Thus, improvements in early diagnosis and molecular testing are important strategies to address the ethnic disparity in lung cancer outcomes.

Following confirmation by staging imaging, an invasive biopsy of tumour tissue is taken for pathological analysis. Tumour molecular testing for an actionable mutation can only be performed if there is sufficient tumour material remaining. This process is dependent on access to healthcare where these specialised biopsy procedures and pathological assessments can be performed, which disadvantages patients with poor access to healthcare or those from regional areas. Furthermore, biopsies can be complicated by pneumothoraces, bleeding, hospitalization and even intubation at rates as high as 16% in some case-series [17]. Hence, a technology that is more widely available, and less reliant on specialist hospital staff could improve the diagnostic pathway for patients with suspected lung cancer.

The analysis of ctDNA by involves a simple blood draw to identify actionable mutations is a promising future diagnostic pathway in lung cancer [15, 18, 19]. In comparative studies of invasive biopsies and ctDNA, ctDNA can identify an additional 20% of actionable mutations compared to biopsied tissue [18-20]. There are a number of testing platforms and assays available, ranging from detection the presence of the most common oncogene, i.e. EGFR mutations, to comprehensive NGS testing of hundreds of genes simultaneously.

Techniques such as droplet digital polymerase chain reaction (ddPCR) assays have been validated to give rapid detection of genes of interest in other cancers such as melanoma [21]. These ddPCR assays are also available for the detection of EGFR mutations in lung cancer but thus far have mainly been used in the research setting. Predesigned BioRad ddPCR assays will allow the detection of the exon 21 (L858R) mutation as well as the simultaneous detection of 15 common mutations that can occur in exon 19 of the *EGFR* gene[22]. The presence of positive droplets for within this assay would provide genomic evidence that the patient would be sensitive to an *EGFR* inhibitor. These assays need to be validated in the clinical

setting but potentially it could provide rapid detection of the most commonly mutated gene that is relevant to treatment decisions. Similar ddPCR assays also exist for common *ALK* rearrangements but again, this need to be clinically validated.

More extensive genomic profiling is already in validated in the clinical setting but these commercial comprehensive NGS panels such as *Guardant360* are extremely expensive (approximately NZD$4000/sample) and evaluate a large number of mutations, in excess of what is needed to identify actionable mutations for lung cancer. The high cost and access requirements of these commercial tests may potentially perpetuate inequities in the care available to lung cancer patients in Aotearoa New Zealand. Taken together, these factors call for a bespoke lung cancer-directed panel that can detect actionable mutations and is reliable and cost-effective for the New Zealand setting.

Thus, rapid detection of actionable mutations in plasma could reduce the diagnostic process from weeks to days, reduce the cost of testing by eliminating the morbidity of invasive tissue biopsy and improve access to diagnostic services [17]. This in turn would enable patients with actionable mutations to start on treatment sooner, facilitate advanced care planning for those without an actionable mutation. In the future, availability of cost-effective local ctDNA testing may promote equity in cancer care for patients in geographically remote regions, and for the large number of patients unable to privately fund expensive commercial ctDNA testing. Importantly, it may allow a deliberate focus on benefit of ctDNA technologies for Māori and Pacific patients.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**
Primary Objective To assess the feasibility of ctDNA to identify actionable mutations in patients with suspected advanced lung cancer	1) Recruitment rate over study period (12 months) 2) Proportion of patients with reportable ctDNA samples

Secondary Objective 1) To identify the turnaround time for ctDNA test as a diagnostic procedure for advanced lung cancer 2) To assess patients' acceptability of the ctDNA test and impact on patient care planning 3) To assess clinicians' experience of the use of ctDNA as a diagnostic process 4) Survival at 3 months	1) Turnaround time from time of blood test collection to result being fed back to clinician 2) Patients' response to questionnaire 3) Clinicians' response to questionnaire – two timepoints, one on the impact on the logistics/therapeutic relationship at the time of diagnostic work up; second part at the time of results being fed back 4) Survival 3 months after enrolment into study

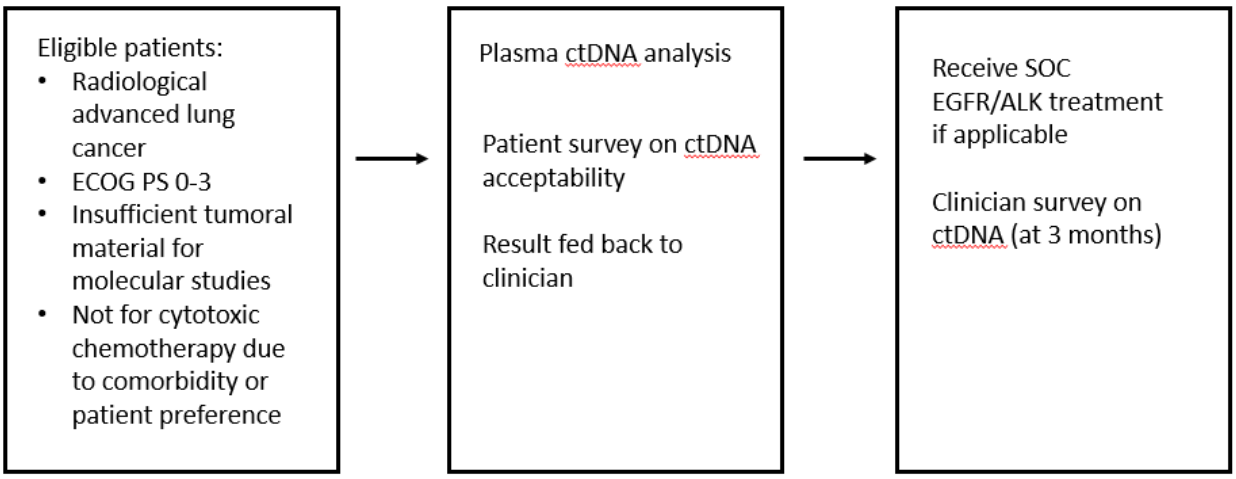
7. TRIAL DESIGN

This is a single-arm phase II pilot feasibility study of ctDNA in the diagnosis of advanced lung cancer in the New Zealand setting.

Eligible patients invited to participate in the study and will provide written informed consent. Standard of care clinical information will be collected. Consented patients will have blood taken for ctDNA analysis. The ctDNA analysis will be performed using three methods: 1) ddPCR for *EGFR* and *ALK* mutations and 2) lung cancer focussed NGS panel and 3) commercial comprehensive genomic profiling using the *Guardant360* assay. Patients will be asked to complete a questionnaire on the acceptability of the ctDNA test and selected patients will be invited to participate in a semi-structured interview about the use of ctDNA in the diagnostic process.

The results of the genomic analyses will be reported back to referring clinician, noting that these tests do not yet carry New Zealand clinical accreditation. Clinicians can then choose whether these test results contribute to treatment decisions in consultation with the patient, though this is not mandated in the study protocol.

At 3 months after study enrolment, there will be a non-contact follow up of survival and clinician questionnaire.



Schema of trial design. ECOG PS, European cooperative oncology group performance status; ctDNA, circulating tumour DNA; SOC, standard of care

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Participants with suspected advanced/metastatic lung cancer who are unable to obtain a diagnostic biopsy or who are unable to have cytotoxic chemotherapy.

8.2. Inclusion Criteria

1. Participant is willing and able to give informed consent for participation in the trial.
2. Male or female, aged 18 years or above.
3. Radiological advanced lung cancer (distant metastases as per AJCC 8th edition TNM staging, stage M1a, M1b or M1c)
4. Radiologist confirmed suspicion of malignancy on chest X-Ray (CXR) or computerised tomography (CT) and clinician opinion likely lung cancer primary
5. Not suitable for cytotoxic chemotherapy but fit for molecularly targeted treatment, due to patient comorbidity, performance status or patient preference
6. Unable to pursue molecular testing of a histological sample
    a. Due to anatomical location/risk of complications or,
    b. Due to patient preference or,
    c. Due to insufficient material for molecular testing
7. Life expectancy expected more than 4 weeks
8. In the Investigator's opinion, is able and willing to comply with all trial requirements.
9. Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

8.3. Exclusion Criteriad

The participant may not enter the trial if ANY of the following apply:

- European Cooperative Oncology Group Performance status (ECOG PS) 4
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

9. TRIAL PROCEDURES

Summary of procedure:

Procedure	Screening	Active study Period	Follow up month 3
Written informed consent	x		
Demographics	x		
Medical history	x		
Physical exam	x		
Laboratory tests			
Radiology reports e.g. CXR, CT	x		
Blood tests for ctDNA		x	
Patient acceptability survey + semi-structured interval		x	
Clinician acceptability survey		x	x
Genomic results to clinician		x	
Survival status			x

Consented patients will undergo screening and collection of standard of care clinical data (as below). Data collected will include basic demographics (e.g. age, sex, and ethnicity) and relevant clinicopathological data (e.g. disease staging, treatment details). Recruited participants will be assigned a unique study ID and all data will be de-identified and stored on password-protected secure RedCap database hosted by the University of Otago Server. Only the researchers directly involved in recruitment and collection of clinical data will have access to identifiable information; all samples will be labelled with the participants study ID.

Blood collected will be collected for ctDNA analysis prior to treatment commencement[23.] In brief, approximately 40 mL of blood will be collected in tubes containing a cell-stabilising reagent e.g. Streck tubes [24]. A karakia is offered to patients at the time of blood collection. The blood will be taken to the local laboratory (Wellington or Auckland Laboratories as listed in the Data and Tissue Management Plan) for processing into plasma within 7 days of blood collection. Plasma samples will be immediately frozen and stored at -80ºC until ctDNA isolation using the Qiagen Circulating Nucleic Acid kit according to manufacturer's protocol. ctDNA samples will be batched and shipped to the UOA laboratories for ddPCR EGFR and ALK testing as well as the lung cancer-focussed NGS protocol. A portion of blood will be sent directly from the local laboratory to the US for the comprehensive Guardant360 Assay (see below).

The University of Auckland testing will include the use of ddPCR as well as the lung cancer focused NGS panel. The ddPCR assays will cover exon 19 and 21 (actionable mutations), EGFR T790M resistance mutation, as well as the three most common ALK-ELM4 partners (variant 1, 2, and two isoforms of 3). The lung-focussed NGS panel will cover the nine oncogenes relevant to lung cancer treatment including: *EGFR, ALK, BRAF, KRAS, MET, NTRK1/2/3, RET, ROS1,* and *ERBB2*. The comprehensive genomic profiling with the Guardant360 assay will cover 83 cancer related genes including the nine aforementioned druggable oncogenes (*Appendix A, Table 1*).

The results of the ctDNA testing will be fed back to the responsible clinician in a report, which notes that the ctDNA test methods and reports, while scientifically validated, are not yet clinically accredited. A

decision about whether to use the ctDNA information in treatment decisions will be made by the oncologist in consultation with each patient. It is anticipated that ctDNA will detect EGFR mutations in 10%-15% of tested patients and ALK mutations in 3% of tested patients, equating to approximately 7 patients out of the recruited 45 patients who would receive targeted treatment as a result of the study.

There is an uncommon (reported as 1% in a large U.S. based study) chance of detecting a gene that is highly associated with an increased risk of an inherited cancer (i.e. a germline mutation) [25]. The finding would be discussed at a Molecular Tumour Board to confirm its clinical relevance. The finding would be need to be validated with a clinically accredited test, and then reported back to the clinician and the patient or their representative. The patient and their family would be offered a referral to the genetics services for genetic counselling and further germline-specific mutation testing.

Patients will both be asked to complete a questionnaire at time of plasma collection, about the acceptability of ctDNA testing, including its impact on advanced care planning. Findings of the ctDNA results will be fed back to the treating health professional as soon as it becomes available so that appropriate management can be undertaken, such as the initiation of targeted treatment or facilitation of palliative care. Selected patients (between 10-15 patients) will be invited to participate in a semi-structure interview about the use the ctDNA in the diagnostic process for their lung cancer.

At 3 months, there will be a non-contact assessment of patient survival from medical records, where the date of death or date of last contact with their clinician will be recorded. Clinicians will be surveyed at that time to assess the impact of results on the therapeutic decision making.

9.1. Recruitment

Patients will be recruited via the respiratory department at Te Whatu Ora Capital, Coast and Hutt Valley and Te Whatu Ora Te Toka Tumai Auckland with referrals from primary care providers, emergency departments, hospital specialists or the lung cancer multi-disciplinary team meeting. Currently the standard diagnostic investigation of advanced lung cancer is performed primarily through the coordination of internal medicine or respiratory departments. Patients will be identified by the treating clinicians and referred to the study team if the patient is eligible.

9.2. Screening and Eligibility Assessment

Eligibility will be determined using inclusion and exclusion criteria. Patients will be given a patient information and consent form at their initial assessment. The written consent will be confirmed on a separate visit. Once patient consent is obtained, blood can be taken for processing for ctDNA analysis as per study procedure to minimise the number of appointments for the patient.

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

9.4. Registration

Patients will be registered on a password-secured RedCap database by the study team. The study team will be notified by email of any new participations to the study.

9.5. Blinding and code-breaking

There is no blinding or code-breaking for this study.

9.6. Baseline visit

- Age, self-identified ethnicity, performance status (ECOG), presenting symptoms and duration
- Records of previous attempts at obtaining histological diagnosis, including sputum cytology, previous bronchoscopies, endoscopic bronchial ultrasound, percutaneous biopsy, liquid biopsies
- Standard of care physical examination including cardiovascular, pulmonary, abdominal, neurological exam findings will be recorded if available
- Date of staging radiological imaging including CXR, CT reports
- Date of diagnosis of metastatic disease (first imaging to show suspected metastatic cancer, either CXR or CT)
- Radiological stage of disease using American Joint Committee on Cancer 8th edition for TNM staging, including record of major organs involved with metastatic disease, including: brain, pulmonary, liver, bone
- Routine blood tests such as full blood count, serum sodium, potassium, creatinine, corrected-calcium, phosphate, magnesium, bilirubin, alanine phosphatase, aspartate aminotransferase, albumin will be recorded if available
- Referring clinician contact details

9.7. Subsequent Visits

The study team will not make any further visits with the patient.

The study team will return the results of the genomic analysis to the referring clinician by email and a report will be provided of any actionable mutations detected from the ctDNA analysis.

9.8. Sample Handling

9.8.1 Sample handling for trial purposes

Up to 40mL of patient peripheral blood samples will be collected in in Streck collection tubes. The cell-save tubes will be processed within 7 days. The blood samples will be centrifuged at 2,000 xg for 10 minutes at room temperature, plasma transferred to a clean tube and centrifugation repeated. The resulting supernatant will be stored in 2 mL aliquots at -80°C, and a buffy coat layer will also be collected and stored at -80°C.

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

- Inability to comply with trial procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

Participants may have the following three options for withdrawal:

1) Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.

2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal. Patient can choose whether their analysed result can be reported back to their clinician.

3) Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

9.10. Definition of End of Trial

At 3 months after study enrolment, there is one non-contact follow up of survival outcome (date or death or date of last contact with clinician). A clinician will be asked to provide a questionnaire about the ctDNA testing, and whether it impacted on clinical decision making. This is the end of the trial.

10. TRIAL INTERVENTIONS

1) ctDNA collection, analysis and reporting of results
2) Patient questionnaire/survey
3) Clinician questionnaire/survey

11. STATISTICS

11.1. Statistical Analysis Plan (SAP)

For data analysis, the primary outcome of the study is the patient recruitment rate over the study period (12 months), as well as the proportion of patients with reportable ctDNA samples. Reportable ctDNA samples is defined by:

1) Oncogenic mutations detected (where an oncogenic mutation is identified);
2) Mutation not detected and;
3) Non-diagnostic sample (for a range of reasons including inadequate plasma, insufficient DNA).

The cost of commercial comprehensive genomic testing is $4000/sample and $400 per sample for the UOA ctDNA panel. Given these significant cost restraints, we expect an achieved sample size of 45 patients has 80% power to rule out a proportion of less than 70%, assuming the proportion with reportable samples is 85% (as per the seminal study of ctDNA testing in lung cancer)[20]. Data from our feasibility study will be able to inform future paired proportions comparisons using the McNemar Test to validate the lung cancer focussed ctDNA panel.

The secondary outcomes are the turnaround time to test result, patient and clinician survey of ctDNA acceptability as well as patient survival 3 months after enrolment into study. These secondary outcomes are crucial to the implementation of ctDNA testing in lung cancer in NZ. While overseas studies have demonstrated a reduction in turnaround times from 15-21 days to 9 days in large academic centres [19, 20], we expect this improvement to be even greater, given the diagnostic process currently takes months[3]. In other studies the rates of actionable mutations are quoted as 25% but this again needs to be validated given our limitations in treatment options of only having funded treatments for EGFR and ALK mutations.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), RAG-M, and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

14.5. Expenses and Benefits

Participants will be not be reimbursed for participation in the study but travel costs of $NZD50 will be provided.

15. FINANCE AND INSURANCE

15.1. Funding

This study has received funding from New Zealand Society of Oncology (Roche Translational Research Fellowship), University of Otago Deans Research Grant and Health Research Council Health Delivery Research Activation Grant and Health Research Council Emerging Research First Grant.

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17. APPENDIX A: SUPPLEMENTARY MATERIALS

Table 1. List of genes tested in the Guardant360 assay

AKT1	*CCND1*	*DDR2*	*GATA3*	*KEAP1*	*MSH2*	*NTRK2*	*RB1*	*TP53*
ALK	*CCND2*	*EGFR*	*GNA11*	*KIT*	*MSH6*	*NTRK3*	*RET*	*TSC1*
APC	*CCNE1*	*ERBB2*	*GNAQ*	*KRAS*	*MTOR*	*PALB2*	*RHEB*	*VHL*
AR	*CDH1*	*ESR1*	*GNAS*	*MAP2K1*	*MYC*	*PDGFRA*	*RHOA*	
ARAF	*CDK12*	*EZH2*	*HNF1A*	*MAP2K2*	*NF1*	*PIK3CA*	*RIT1*	
ARID1A	*CDK4*	*FANCA*	*HRAS*	*MAPK1*	*NFE2L2*	*PMS2*	*ROS1*	
ATM	*CDK6*	*FBXW7*	*IDH1*	*MAPK3*	*NOTCH1*	*PTEN*	*SMAD4*	
BRAF	*CDKN2A*	*FGFR1*	*IDH2*	*MET*	*NPM1*	*PTPN11*	*SMO*	
BRCA1	*CHEK2*	*FGFR2*	*JAK2*	*MLH1*	*NRAS*	*RAD51D*	*STK11*	
BRCA2	*CTNNB1*	*FGFR3*	*JAK3*	*MPL*	*NTRK1*	*RAF1*	*TERT*	

18. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, RAG-M