Title

Trial Design
Multi-centre multi-arm phase II trial, each arm testing an experimental drug in a population stratified by multiple pre-specified target biomarkers using a Bayesian adaptive design.

New drug-putative biomarker arms and no actionable genetic change cohorts will be added to the protocol by substantial amendment throughout the trial.

Trial Objectives
This is a rolling phase II trial of molecularly targeted anti-cancer agents for patients with locally advanced or metastatic NSCLC selected for molecular phenotype appropriate to the mechanism of action of each agent, with the purpose:

- To detect whether there is a signal of drug activity sufficient to justify further investigation in that molecularly-defined group.
- To collect tissue linked to clinical outcome data for future exploratory analysis to investigate the molecular phenotype of tumours in responding versus non-responding patients and to further develop the clinical diagnostic test necessary to support further investigation of the agent in the relevant molecularly-defined group.
- To identify predictive biomarkers for activity of the various drugs used in the various molecular cohorts.
- To determine the mechanisms of resistance to the target therapies utilised.
Outcome Measures
- Best objective response rate (ORR)
- Best percentage change in sum of target lesion diameters (PCSD)
- Time to progression (TTP)
- Progression-free survival time (PFS)
- Overall survival time (OS)
- Toxicity

Patient Population
Locally advanced or metastatic NSCLC patients, who have previously consented to molecular profiling of their tumours.

Trial Duration
Minimum of 2 years. There is no current limit on trial duration given that this is a rolling adaptive trial design which explicitly allows for the introduction of new drug/biomarker trial arms during the running of the trial.

Sample Size
The target sample size for each drug-putative biomarker cohort is 30 patients but the adaptive design allows decisions to be made with any number of patients. The sample size for each sequential cohort in the no actionable genetic change arm will be determined for each drug individually as they are introduced into the sequential pipeline.

Core Key Inclusion Criteria
- Patients must have completed all standard of care therapy that the treating oncologist thinks is appropriate. As a minimum patients must have failed one or more lines of treatment (either radiological documentation of disease progression or due to toxicity).
- Consented and provided an adequate specimen to completely characterise the molecular phenotype of the tumour in SMP2 (see protocol for definition of an adequate sample).
- Histological or cytologically confirmed NSCLC stage III (not suitable for radical radiotherapy or surgery) or stage IV. This includes patients who may not have clear morphology, but IHC strongly support either squamous cell carcinoma (p63 positivity) or adenocarcinoma (Thyroid transcription factor 1 [TTF1] positivity). If a physician and pathologist are convinced after multi-disciplinary review that the patient has stage III or IV NSCLC but where all the IHC is negative and the morphology does not distinguish a specific sub-type, these patients will be eligible for non-histology specific cohorts.
- CT scan of head, chest and abdomen within 28 days of treatment demonstrating measurable disease as per RECIST version 1.1.
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1 with no deterioration over the previous 2 weeks.
- Adequate haematological, hepatic and renal function with 7 days of treatment (see protocol for full criteria)
- Age ≥ 18 years.
- Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses.
Core Key Exclusion Criteria

- Major surgery (excluding placement of vascular access), chemotherapy, radiotherapy, any investigational agents or other anti-cancer therapy within 4 weeks prior to treatment.
- Nausea, vomiting, chronic gastrointestinal diseases (e.g. inflammatory bowel disease) that would preclude adequate absorption.
- Any psychological, familial, sociological or geographical condition hampering protocol compliance.
- Concurrent malignancies or invasive cancers diagnosed within past 5 years except for adequately treated basal cell carcinoma of the skin and in situ carcinoma of the uterine cervix.
- Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
- Any unresolved toxicity of grade 2, 3 or 4 from previous treatment (excluding alopecia) at Registration.
- Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 28 days prior to registration.
- As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus. Screening for chronic conditions is not required.
- Patients and patients with partners of childbearing potential not willing to use effective contraception during the trial period and for at least 90 days after completion of treatment.
- Female patients of child bearing potential should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to registration.
- Female patients of non-child-bearing potential are excluded unless they fulfil one of the following criteria at screening:
  - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
  - Women aged under 50 years old would be consider postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for the institution.

The above lists are not exhaustive and full eligibility criteria can be found in the protocol. Arm-specific eligibility criteria (including cardiac exclusion criteria) can also be found in the protocol.

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<table>
<thead>
<tr>
<th>Arm</th>
<th>Investigational Medicinal Products</th>
<th>Cohort Number</th>
<th>NSCLC Histology</th>
<th>Molecular Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AZD4547 – Fibroblast growth factor receptor (FGFR) Inhibitor</td>
<td>A1</td>
<td>NSCLC</td>
<td>FGFR2 &amp; 3 mutation</td>
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<tr>
<td>B</td>
<td>AZD2014 – Mammalian target of rapamycin complex (MTORC)-1/2 Inhibitor</td>
<td>B1</td>
<td>NSCLC</td>
<td>Tuberous Sclerosing complex (TSC)-1/2 mutation</td>
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<td></td>
<td>B2</td>
<td>NSCLC</td>
<td>Liver Kinase (LK)-B1 mutation TIER1</td>
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<td></td>
<td>B3</td>
<td>NSCLC</td>
<td>Liver Kinase (LK)-B1 mutation TIER2</td>
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<td>C</td>
<td>Palbociclib – Cyclin dependent kinase (CDK)-4/6 Inhibitor</td>
<td>C1</td>
<td>Squamous Cell Carcinoma (SCC)</td>
<td>Retinoblastoma (Rb)-proficient (with no loss of Rb function either by mutation or deletion) and homozygous p16 (CDKN2A) loss</td>
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<td>C2</td>
<td>Adenocarcinoma (ADC)</td>
<td>Retinoblastoma (Rb)-proficient (with no loss of Rb function either by mutation or deletion) and homozygous p16 (CDKN2A) loss</td>
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<td>C3</td>
<td>NSCLC</td>
<td>Rb-proficient &amp; (with no loss of Rb function either by mutation or deletion) CDK4 amplification</td>
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<td>C4</td>
<td>NSCLC</td>
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<td>C5</td>
<td>ADC</td>
<td>Rb-proficient &amp; (with no loss of Rb function either by mutation or deletion) KRAS mutation (No concomitant PIK3CA mutation or amplification, no PTEN mutation or homozygous deletion, no AKT mutation, no EGFR mutation and no TSC1/2 mutation)</td>
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<tr>
<td>D</td>
<td>Crizotinib – Anaplastic lymphoma kinase (ALK) Inhibitor</td>
<td>D1</td>
<td>NSCLC</td>
<td>MET amplification</td>
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<tr>
<td></td>
<td></td>
<td>D2</td>
<td>NSCLC</td>
<td>ROS1 gene fusions</td>
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<td>E</td>
<td>Selumetinib – Mitogen activated protein kinase kinase (MEK) Inhibitor &amp; Docetaxel</td>
<td>E1</td>
<td>SCC</td>
<td>Neurofibromin (NF)-1 mutation</td>
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<td>E2</td>
<td>ADC</td>
<td>NF1 mutation</td>
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<tr>
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<td></td>
<td>E3</td>
<td>ADC</td>
<td>NRAS mutation</td>
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<td>NA</td>
<td>MEDI4736 – Programmed death-ligand (PD-L1) Inhibitor</td>
<td>NA1</td>
<td>NSCLC</td>
<td>No actionable genetic change for other trial arms</td>
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