Deciphering **A**fatinib **R**esponse and Resistance **W**ith **IN**tratumour Heterogeneity

STUDY DESIGN & AIM

DARWIN1 is an open label, multi-centre single arm phase II trial of afatinib in patients in the TRACERx study who have relapsed NSCLC and either a sensitising EGFR mutation or a HER2 mutation.

The overall aim is to explore whether patients with clonal dominance of EGFR/HER2 mutation have better outcomes after treatment with afatinib than those with subclonal mutations.

ENDPOINTS & ANALYSIS

Primary Endpoint:

- Median progression free survival (PFS)

Key Secondary Endpoints:

- Overall survival
- Time on treatment
- Time-to-progression
- Tumour Response, based on RECIST v1.1
- Toxicity based on CTCAE v4.03 (including dose reductions, interruptions, modifications and exposure)

Exploratory Analyses:

- Exploratory assessments include interrogation of recurrence and progression biopsies to decipher the molecular basis for afatinib resistance in combination with analyses of CTCs/cfDNA as well as CT imaging heterogeneity analyses.

TISSUE AND BLOOD SAMPLES

- Biopsy of site of recurrence (consented as part of TRACERx or separately for non-TRACERx patients) prior to starting afatinib
- Biopsy at progression (additional consent form required)
- cfDNA plasma samples at pre-cycle 1 (baseline), pre-cycle 2 and alternate cycles until (and including) progression
- CTC blood samples at pre-cycle 1 (baseline), pre-cycle 4 and progression

Please refer to the DARWIN1 protocol, laboratory manual and samples summary for details.
Please note: additional samples are also required as part of the TRACERx study. Please refer to the TRACERx protocol, trial specific procedures and samples summary for details.

SUMMARY OF ELIGIBILITY CRITERIA

- Must have biopsy of site of recurrence (consented as part of TRACERx or consented separately for non-TRACERx patients)
- Sensitising EGFR/HER2 mutation identified in the primary surgical sample or biopsy
- Non-TRACERx patients must have at least two archival tissue/DNA samples of their disease available.
- ECOG performance status 0-3
- No previous exposure to an EGFR TKI (other than afatinib) or HER2 targeted therapy
- Measurable disease by RECIST v1.1. Patients without measurable disease may be eligible following discussion with the CI and UCL CTC but will not count towards the primary PFS endpoint.
- At least 18 years of age
- Anticipated life expectancy of at least three months
- Adequate organ function as defined in the protocol
- No prior surgical procedures or medical comorbidities that affect GI absorption
- No current or pre-existing interstitial lung disease
- No significant or recent acute GI abnormalities with diarrhoea as a major symptom
- No known hypersensitivity to afatinib or to any of the excipients
- No rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- No anti-cancer therapy within 14 days prior to start of afatinib, except radiation therapy
- No known HIV, HBV, HCV or syphilis infection
- No history of other malignancy (see protocol for exceptions)
- No cardiac abnormalities (see protocol for list)
- No conditions that may preclude informed consent or protocol compliance
- No pregnant, lactating or actively breastfeeding females.
- Women of child bearing potential must have a negative pregnancy test within 14 days prior to starting trial treatment.
- Patients of childbearing potential/able to father a child must be willing to use highly effective contraceptives during the trial and for one month after end of treatment

This is an abbreviated summary of eligibility criteria. Please refer to the current DARWIN1 protocol for full list of inclusion/exclusion criteria.

CONTACT DETAILS

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Trial Schema

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TRACERx/ non-TRACERX patients

Disease recurrence

EGFR/HER2 mutation positive

Consent to DARWIN1

Baseline assessments

Registration

NB. Biopsy of site of recurrence must be done prior to starting treatment (consent through TRACERx or consent separately for non-TRACERx patients)

Start treatment (within 1 week of registration): Afatinib PO daily in 28 day cycles

Assessments: Week 2, 4 (pre-cycle 2) and four-weekly thereafter

Tumour Response: CT scan + RECIST v1.1 Week 4 (pre-cycle 2) and eight-weekly thereafter

Translational Samples:
- cfDNA/cExosomes at pre-cycle 1, pre-cycle 2 and then every 8 weeks, and progression
- CTC blood samples at pre-cycle 1, pre-cycle 4 and progression

Stop treatment if unacceptable toxicity, intercurrent illness or patient/clinician decision

Monthly follow up until progression and resolution or stabilisation of any toxicities

Patient follow-up will continue under the TRACERx protocol as long as TRACERx remains open for TRACERx patients or continue under local routine follow up for non-TRACERx patients

Response/stable disease

Progression (stop treatment*)

Monthly follow up until resolution or stabilisation of any toxicities

Translational Samples: cfDNA and CTC blood and biopsy (separate consent)

*Afatinib treatment may continue beyond progression if the investigator believes the patient would derive clinical benefit from continuing treatment and continuation is agreed as per DARWIN1 protocol section 8.3. Patients continuing afatinib will also continue trial assessments.