Deciphering Antitumour Response and Resistance With INtratumour Heterogeneity

STUDY DESIGN & AIM

DARWIN2 is a phase II, multi-centre, non-randomised, molecularly stratified trial for NSCLC patients to study tumour heterogeneity using genomic analysis.

This trial aims to explore whether mutational burden and neo-antigen repertoire predict for improved progression free survival with anti-PDL1 mAb immunotherapy for those patients with stage IIIB/IV NSCLC (in patients whose tumour lacks an actionable mutation).

For those patients with actionable BRAFV600 mutations, HER2 amplification and HER2 IHC 3+ or ALK/RET gene fusions this trial aims to assess the role of clonal dominance on the mechanism of action and response to vemurafenib, trastuzumab emtansine and alemtuzib respectively.

ENDPOINTS

Primary Endpoint:

- To compare the efficacy of MPDL3280A (Atezolizumab), as measured by investigator-assessed progression free survival according to:
  I. Intra-tumour heterogeneity as assessed using an intratumour heterogeneity score
  II. Genomic instability as assessed using a weighted genome instability index (wGII)
  III. Neo-antigen burden
  IV. Mutational burden
- PFS is defined as the period between the date of registration to the date of progression or death (whichever occurs first)
- Overall Survival (OS is defined as the time between the date of enrolment and the date of death due to any cause)

Secondary Endpoints:

- ORR – Investigator assessed according to RECISTv1.1
- Other time to event outcomes, including time to progression, disease free survival and duration of response, disease control benefit (>6 months)
- Toxicity, including dose reductions, interruptions modifications and exposure

TISSUE AND BLOOD SAMPLES

- Biopsy of site of recurrence (consented as part of TRACERx for applicable patients; for non-TRACERx consent must first be obtained) prior to starting any treatment. Non-TRACERx patients must have two tissue/DNA samples of their disease available.
- Biopsy at progression (if patient consents)
- cfDNA plasma samples at pre-cycle 1 (baseline), post-cycles 2, 4, 6, 8, 12, 16, 20, at end of treatment, and on progression for patients on Arm 1
- cfDNA plasma samples at pre-cycle 1 (baseline), post-cycles 1, 2, 4, 6, and every 3 cycles thereafter, and on progression for patients on Arms 2, 3 or 4
- CTC blood samples at pre-cycle 1 (baseline), post-cycle 2 and progression for all patients

Please refer to the DARWIN2 protocol and laboratory manual and 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

- Multi region sequencing data of the primary tumour available. Non-TRACERx patients must have two tissue/DNA samples of their disease available
- Must be willing to have biopsy of relapsed disease prior to starting any treatment
- Arm 1: Absence of any actionable mutation
- Arm 2: Presence of BRAFV600 mutation
- Arm 3: Presence of ALK/RET gene fusion and ALK IHC+
- Arm 4: Presence of HER2 amplification and HER2 IHC 3+ only
- Absence of sensitizing EGFR mutation (see protocol for exceptions)
- ECOG performance status 0-2 for Arms 1-3, or 0-1 for Arm 4
- Measurable disease by RECIST v1.1. Patients without measurable disease may be eligible following discussion with the CI and UCL CTC
- Anticipated life expectancy of at least three months
- Able to swallow and retain oral medication (Arms 2&3)
- Adequate organ function
- Unsuitable for radical radiotherapy
- No anti cancer therapy within 14 days prior to registration
- Arm 2: Previous BRAF inhibitor
- Arm 3: Pre-existing EGFR mutation
- Arm 4: No EGFR mutations available.
- No current or pre-existing interstitial lung disease
- No known hypersensitivity to any study IMP or to any of the excipients
- No known HIV, HBV, HCY or syphilis infection
- No history of other malignancy (see protocol for exceptions)
- No symptomatic brain metastases
- No severe symptomatic arrhythmias (excluding atrial fibrillation)
- No cardiac abnormalities
- No conditions that may preclude informed consent or protocol compliance
- No pregnant, lactating or actively breastfeeding females
- 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
- Arm 1: No treatment with corticosteroids or other systemic immunosuppressive medications 2 weeks prior to registration, or anticipated requirement for such medications during the trial (see protocol)
- Arm 2, 3 and 4: No patients taking medication known to prolong QT interval 2 weeks prior to registration
- Arm 2: Previous BRAF inhibitor therapy

Please refer to the DARWIN2 protocol for full list of inclusion/exclusion criteria

CONTACT DETAILS

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Sponsor: University College London
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DARWIN2 study summary v3.0  01/10/2018
**Arm 1:** No actionable mutation

- Lung TRACERx enrolled patient or patients with multi-region sequencing data or two available tissue/DNA samples of their disease.
  - primary tumour surgically resected
  - completed adjuvant treatment
  - presents with first relapse (locoregional/metastatic)

- Consents to biopsy of relapsed disease
  - testing for actionable mutation
  - RECIST (v1.1) assessable disease on imaging within 30 days

- No actionable mutation

- Consent to DARWIN2 (Arm 1)

- MPDL3280A (Atezolizumab) 1200mg – (every 3 weeks) for maximum of 24 cycles

  - Imaging & response assessment after cycles 2, 4, 6, 8, 12, 16, 20 and at end of treatment.
  - Clinician assessment and blood samples every cycle

  - PD

  - Re-biopsy

  - Continue on MPDL3280A (Atezolizumab) for 16 cycles or until progression

  - End of treatment assessment

  - Trial follow up monthly until stabilisation of AEs

**Arm 2 – BRAFV600:**

- Lung TRACERx enrolled patient or patients with multi-region sequencing data or two available tissue/DNA samples of their disease.
  - primary tumour surgically resected
  - completed adjuvant treatment
  - presents with first relapse (locoregional/metastatic)

- Consents to biopsy of relapsed disease
  - testing for actionable mutation
  - RECIST (v1.1) assessable disease on imaging within 30 days

- BRAF V600
  - BRAF V600 mutation positive in Miseq-Lung cancer gene panel report

- Consent to DARWIN2 (Arm 2)

- Vemurafenib 960mg twice daily

- Imaging & response assessment every 2 cycles for 6 cycles then every 3 cycles

  - Clinician assessment and blood samples every cycle

  - PD

  - SD/PR/CR

  - Re-biopsy

  - Continue on Vemurafenib until progression or unacceptable toxicity (Reevaluate every 2 cycles for 6 cycles then every 3 cycles)

  - End of treatment assessment

  - Follow up monthly (until resolution or stabilisation of AEs)

  - TRACERx patients: revert to TRACERx follow-up
  - Non-TRACERx patients: revert to routine follow-up. UCL CTC informed of patient’s death

TRACERx patients: revert to TRACERx follow-up
Non-TRACERx patients: revert to routine follow-up. UCL CTC informed of patient’s death
**Actionable mutation: Arm 3 – ALK/RET gene rearrangement:**

Lung TRACERx enrolled patient or patients with multi-region sequencing data or two available tissue/DNA samples of their disease.
- primary tumour surgically resected
- completed adjuvant treatment
- presents with first relapse (locoregional/metastatic)

**ALK/RET gene rearrangement**
ALK positive IHC or positive RET FISH

**Consents to biopsy of relapsed disease**
- testing for actionable mutation
- RECIST (v1.1) assessable disease on imaging within 30 days

**Alectinib 600mg twice daily**

**Imaging & response assessment**
- every two cycles for first 6 cycles then every 3 cycles
- Clinician assessment and blood samples every cycle (fortnightly for first 2 cycles)

**PD**

**Re-biopsy**

**End of treatment assessment**

**Follow up monthly until resolution or stabilisation of AEs**

**TRACERx patients**: revert to TRACERx follow-up
**Non-TRACERx patients**: revert to routine follow-up. UCL CTC informed of patient’s death

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**Actionable mutation: Arm 4 – HER2 amplification and HER2 IHC 3+:**

Lung TRACERx enrolled patient or patients with multi-region sequencing data or two available tissue/DNA samples of their disease.
- primary tumour surgically resected
- completed adjuvant treatment
- presents with first relapse (locoregional/metastatic)

**HER2 Amplification**
Patients with HER2 IHC 3+ status

**Consents to biopsy of relapsed disease**
- testing for actionable mutation
- RECIST (v1.1) assessable disease on imaging within 30 days

**Trastuzumab emtansine 3.6mg/kg – every 3 weeks**

**Imaging & response assessment**
- every two cycles for first 6 cycles then every 3 cycles
- Clinician assessment and blood samples each cycle.

**PD**

**SD/PR/CR**

**Re-biopsy**

**End of treatment assessment**

**Follow up monthly until stabilisation or resolution of AEs**

**TRACERx patients**: revert to TRACERx follow-up
**Non-TRACERx patients**: revert to routine follow-up. UCL CTC informed of patient’s death