**Non-Interventional Study (NIS) Report Synopsis**

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| NIS Name/Code | D5161R00003 |
| Edition Number | 1.0 |
| Date | 25-Mar-2020 |

# An observational, multicentre, Prospective study to evaluate concordance of detecting EGFR mutation by circulating tumour free DNA versus tissues biopsy in NSCLC(CONCORDANCE)

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| **Study dates:** | **First Subject In:** 16 Aug 2018<br>**Last Subject Last Visit:** 07 Jun 2019 |
| **National/international Coordinating Investigator:** | Dr Senthil Rajappa,<br>Sr consultant Medical Oncologist, Basavatarakam Indo-American<br>Cancer Hospital and Research Institute, Road no 10, banjara hills,<br>Andhra Pradesh 500034 India |

# NIS REPORT SYNOPSIS)

# An observational, multicentre, Prospective study to evaluate concordance of detecting EGFR mutation by circulating tumour free DNA versus tissues biopsy in NSCLC (CONCORDANCE)

**Background/Rationale**:

Tissue testing is recommended in non-squamous advanced Non-Small Cell Lung Cancer (NSCLC) by various guidelines to confirm Epidermal Growth Factor Receptor mutation and treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI). Researchers diagnosed NSCLC in most cases on small tissue samples that may not always be sufficient for EGFR mutational assessment to select patients for first and second generations TKIs therapy. In patients without tissue availability at presentation, the analysis of cell free DNA (cfDNA; also referred to as ctDNA) derived from liquid biopsy samples, in particular from plasma, represent an alternative to provide EGFR mutational testing for treatment decision making. ctDNA mutational analysis is a clinically congruent way to check the presence of EGFR mutations in ctDNA and predict its counter effect to EGFR TKIs.

However, the above observations have not been established in the Indian population. Therefore, this study was aimed to confirm such findings among Indian patients to improve local diagnostic practice, enable wider access to ctDNA mutation testing, and provide more patients with access to therapies personalized to the mutation status of their tumours.

This large multicentre, observational study was designed to investigate the utility of ctDNA for EGFR mutation testing with Next-Generation Sequencing (NGS) in a real-world diagnostic setting in Indian patients.

**Objectives and Hypotheses:**

**Primary Objective:**

To assess the level of concordance between EGFR mutation status obtained from tissue and blood (plasma) based testing.

**Secondary Objectives:**

1. To determine the frequency of EGFR gene mutation in patients with advanced NSCLC (aNSCLC) of adenocarcinoma histology as assessed by the plasma samples.
2. To assess the prevalence of T790M mutation in TKI treatment, naïve NSCLC patients as assessed by the plasma samples.

**Methods:**

**Study design:**

This was a multicentre, prospective, study of EGFR mutation status in advanced NSCLC patients (locally advanced and metastatic disease) with adenocarcinoma histology proposed. We conducted the study at 15 sites from different geographical regions across India. The study targeted to enroll 268 patients over six months. The study had enrolled patients with histologically confirmed, systemic treatment naïve adenocarcinoma metastatic cancer (stage IV). This was a single visit study. No study medication was prescribed or administered as a part of the study procedure.

**Study Population:**

**Inclusion Criteria:**

1. Patients who provided written, informed consent.
2. Patients aged 18 years and older.
3. Newly diagnosed patients with metastatic (stage IV) NSCLC.
4. Histologically confirmed Adenocarcinoma NSCLC patients as per tissue biopsy and tissue sample sent for EGFR mutation analysis OR result for EGFR mutation test is available from the last 28 days from the date of enrolment.
5. A patient who was naïve for any systemic treatment (i.e., no chemotherapy or EGFR-TKI)
6. Provision of a routine blood (plasma) sample.

The prescription of any medicinal product is clearly separated from the decision to include the subject in the study.

**Exclusion Criteria:**

1. Patient with any medical condition that, in the opinion of the investigator, would interfere with the outcome of the study.
2. Patient participating in any other interventional clinical study/trial.

**Exposure:**

This was an observational, prospective study which aimed to capture the data regarding concordance of EGFR mutation. The study did not target to expose patients to any drug.

**Outcomes:**

**Primary Outcome:**

Determine the level of concordance between EGFR mutation status obtained by tissue and blood (plasma) based testing in terms of overall concordance, sensitivity, specificity, positive predictive value & negative predictive value.

**Secondary Outcomes:**

1. To determine the frequency of mutations on Exon 19, 20 & 21 of EGFR gene (including mutation subtypes: exon 19 deletions and the L858R) among study patients as assessed by the plasma samples.
2. To assess the frequency of T790M mutation among study patients.

**Sample Size Estimations:**

Approximately 254 subjects were required to assess the level of concordance of EGFR mutation status obtained by blood (plasma) and obtained by tissue testing by assuming 5 % level of significance. The expected level of concordance in EGFR mutation status obtained by ctDNA (Plasma) and obtained by tissue testing was 89 % (2), the precision of 3.85 %. To achieve the aim of this study, approximately 268 subjects were enrolled considering 5 % dropout rate.

**Statistical Analysis:** Basic summary statistics were used to describe the data to meet the objectives. Descriptive statistics were used for primary and secondary analysis in the study. We calculated the frequency and percentages of patients with EGFR mutation and its subtypes. For the primary objective, the concordance rate, sensitivity, specificity, positive and negative predictive values, and their exact 2-sided 95 % confidence interval for comparing mutation status between tumour and plasma samples were calculated for the evaluable population.

**Results**: A total of 245 subjects were enrolled. The majority [158 (64.5)] of the subjects were males. 75 (30.6%) subjects showed positive mutation status by plasma and 84 (34.3%) showed positive mutation status by tissue testing. The overall concordance of 82.9% existed between tissue and ctDNA (Plasma) based testing. 100% sensitivity of EGFR mutation status between ctDNA (Plasma) and Tissue was examined for EGFR mutation subtypes. Specificity of EGFR mutation subtypes status between ctDNA (Plasma) and Tissue was observed to be

90.1%. Plasma and tissue sample testing detected 1.2 % (03 subjects) and 2.4 % (06 subjects) positive for Exon 20 T790M type EGFR mutation, respectively.

**Conclusions:** Our data in this study provide an initial estimate of concordance between tissue and blood (plasma) based testing. It was found to have a concordance of more than 80% for EGFR mutation subtypes. This data in Indian patients may encourage physicians to opt for convenient testing methods for EGFR mutation detection in newly diagnosed NSCLC patients.