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# The challenge of molecular testing for clinical trials in advanced non-small cell lung cancer patients: Analysis of a prospective database

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ABSTRACT

*Objectives:* Molecular testing has become important in the biomarker program of clinical trials for advanced non-small lung cancer (NSCLC). These tissue samples often have to be analyzed in a central laboratory. We evaluated the turnaround time and possible delay in start of therapy in this process and how often testing resulted in inclusion in a clinical trial.
*Methods:* We reviewed our prospective database on all molecular testing cases for clinical trial suitability in patients with advanced NSCLC between March 1, 2011 and October 31, 2014.
*Results:* 250 patients were considered for biomarker-driven trials. Twenty-three cases did not have further analysis and 20 patients had failure of central biomarker analysis. Results were obtained for 207 (83%) patients. In 91 of 227 (40%) samples sent, a biomarker of interest was documented. This led to 34 (15%) clinical trial inclusions.

The mean waiting time between informed consent and request for tissue sections from the pathology lab and receipt of biomarker result from central lab was 24.4 (SD 13.7) calendar days.
*Conclusion:* While molecular biomarker testing is crucial in many NSCLC trials, our results show that waiting times for central laboratory analysis can cause an important delay in treatment initiation, and even ineligibility for the trial(s) under consideration. Start of therapy based on properly validated local testing, with a posteriori central biomarker testing to guarantee the integrity of the trial, would be more rewarding for quite some patients.



## 1. Introduction

Over the last decade, there has been a major change in the management of advanced non-small cell lung cancer (NSCLC). In an increasing proportion of tumors, a treatable biomarker can be identified, and targeted therapy is preferred over chemotherapy [1]. Biomarker guided therapies offer more effective therapeutic options with less severe side effects and better quality of life. Tyrosine kinase inhibitors (TKI) targeting the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) protein have demonstrated improved clinical outcomes, quality of life and progression-free survival, compared with standard platinum-based chemotherapy [2–4]. The oral administration and mild toxicity profile of TKIs also offer the advantage to start this therapy in elderly patients and those with a poor performance status, patients who would not be candidates for chemotherapy. Routine testing for EGFR mutation and ALK rearrangement in advanced non-squamous NSCLC has become a standard of care in managing advanced NSCLC in clinical practice [5,6], and clinical guidelines now recommend targeted therapy as upfront therapy for these tumors [1].

The growing insight in tumor biology resulted in the identification of different genetic alterations, especially in adenocarcinoma, less frequently in squamous cell carcinoma. The development of new drugs for the treatment of NSCLC shifted towards biomarker driven therapies, with emphasis on molecular analyses in recent clinical trials. A number of less common biomarkers, including mutations (KRAS, BRAF, MET, HER2,. . .) and gene rearrangements or copy number changes (ROS1, MET, RET, . . .) have been identified

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**Table 1**
Selected NSCLC biomarkers of interest.

| NSCLC | mutations | gene abnormality |
|---|---|---|
| adenocarcinoma | EGFR | mutation |
| | ALK | translocation |
| | KRAS | mutation |
| | ROS1 | translocation |
| | BRAF | mutation |
| | MET | amplification and mutation |
| | RET | translocation |
| | HER2 | amplification and mutation |
| | B-catenin | mutation |
| | MEK1 | mutation |
| squamous carcinoma | FGFR1 | amplification |
| | DDR2 | mutation |
| | PIK3CA, AKT1, PTEN | mutation |

(Table 1) and patients with a tumor harboring those biomarkers are included in clinical trials with drugs targeting these oncogene drivers. This targeted approach however implicates that inclusion in clinical trials requires a demonstrated biomarker, often in a central reading, before therapy can be started.

In this study we looked at the turnaround time of molecular testing, in the setting of clinical trials that require central assessment of the biomarker, before therapy can be started.

## 2. Methods

### 2.1. Study design and participants

We analyzed our prospective database on molecular testing for clinical trial suitability in patients with advanced NSCLC, looking at the records between March 1, 2011 (start of the database) and October 31, 2014. All patients included in this database had signed an IRB approved informed consent form for molecular screening in the light of possible clinical trial therapy.

### 2.2. Objectives

The primary objective was to analyze the process and time flow to identify patients with a tumor carrying a biomarker of interest, in the light of a clinical trial. We also examined how many of these patients finally could be included in a biomarker driven trial.

The main endpoint of the analysis was the waiting time between signing informed consent by the patient and receiving the results of the biomarker analysis, needed for the start of therapy. For that purpose, the following time points were defined: T1 (signing of informed consent and request for tissue sections from the pathology lab by the data manager); T2 (receipt of sections and shipment to central lab); T3 (arrival of sections in central lab); and T4 (receipt of biomarker result from central lab).

### 2.3. Statistical methods

Descriptive statistics were used to summarize patient and sample characteristics.

## 3. Results

### 3.1. Patient characteristics

The analysis is based on molecular screening for possible inclusion in nine ongoing clinical trials. All clinical trials requested central confirmation of the biomarker on a formalin fixed, paraffin embedded (FFPE) tumor material before start of therapy, but a new tissue sample was not mandatory. Consequently, a new biopsy was performed only when the archival biopsy was insufficient or deemed to be of uncertain quality.

Two hundred fifty patients were considered for biomarker-driven trials (Fig. 1). Twenty-three cases did not have further analysis, as the request for central molecular testing was cancelled due to insufficient tissue (n = 11), exclusion criterion (n = 10) or patient refusal (n = 2).

Of the remaining 227 patients, there was a failure of central biomarker analysis in 20 patients, due to insufficient quantity of tissue (n = 17) or quality of tissue (n = 3, i.e. decalcification or poor fixation). As expected insufficient quantity of tissue occurred more in archival tissue than in re-biopsies (n = 3 versus n = 14). Failure of central analysis occurred in all kind of samples (endoscopic (n = 13), distant metastasis (n = 4), surgical (n = 1), CT-guided (n = 1) and unknown origin (n = 1)). Reliable results were obtained for 207 patients.

In 91 of 227 (40%) samples sent, a biomarker of interest was documented. This led to 34 clinical trial inclusions. Other patients were no longer eligible due to loss of performance status (n = 20), other exclusion criterion (n = 5), loss of contact (n = 14), or no trial slot available at the appropriate time (n = 18).

### 3.2. Sample characteristics

In the 227 patients, an archival biopsy sample was used in 161, while re-biopsy was necessary in 64 patients. From 2 patients this was unclear, because the sample was from another hospital, where this information could not be retrieved.

Biopsies were obtained with a variety of procedures (Fig. 2): endoscopic (n = 128), computed tomography guided needle biopsy (n = 11), percutaneous biopsy procedure on distant metastases (n = 20), or surgical procedure (n = 53). For 15 patients, we do not know what procedure was performed because they were referred from another hospital, where this information could not be retrieved.

Endoscopic samples were either endobronchial biopsies, radial endobronchial ultrasound guided transbronchial biopsies, endobronchial ultrasound-guided transbronchial needle aspiration blocks (EBUS-TBNA), or pleuroscopy biopsies. Non-surgical samples from distant metastases were clinically, ultrasound or CT guided biopsies of lesions in the liver, muscle, adrenal gland, skin, or peripheral lymph node. Surgical specimens were obtained at the time of previous lung resection surgery, mediastinoscopy, video-assisted thoracic surgery (VATS) biopsy sample, or surgical procedure on a distant metastasis.

### 3.3. Time flow of biomarker results

The focus of our analysis, the mean waiting time between signing of informed consent (T1) and receiving results of the biomarker analysis (T4), was 24.4 (SD 13.7) calendar days (Table 2A). The preparation of the unstained slides by the pathology lab (T2-T1) took about 9.1 (SD 6.8) days, the time of the biomarker testing itself in the central lab (T4-T3) accounted for 12.8 (SD 7.3) days.

Of these 227 patients, 69% were seen at our center, and 31% were referred from another hospital. Waiting times in both groups were very similar, as patients were referred for a possible molecular therapy, and brought their biopsy already on the first visit where the informed consent was signed.

For 17 of 227 (7.4%) patients, repeated sample shipments were needed because of insufficient tumor cells (n = 12), need for extra slices (n = 3) or problems with transport (n = 2). These patients had a longer time interval from informed consent to receiving the biomarker result as compared to patients with only one shipment of tissue (median 55 (SD 24.1) days versus 21.9 (SD 8.8) days) (Table 2B and C).