Role of circulating tumor DNA (ctDNA) from Liquid Biopsy in Early Stage NSCLC Resected Lung Tumor Investigation (LIBERTI)

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INTRODUCTION

The detection of ctDNA after cancer surgery with curative intent may indicate the presence of minimal residual disease and a higher risk for relapse. The Addario Lung Cancer Medical Institute (ALCMI) has launched a multi-center study to evaluate the role of ctDNA in patients with completely resected stage II to III non-small cell lung cancer (NSCLC) using a highly sensitive assay developed by Inivata. This molecular residual disease (MRD) personalized assay is used to detect tumor-specific variants in plasma DNA from patients with NSCLC.

CLINICAL UTILITY OF MRD

Detecting whether or not a patient has residual disease following curative-intent surgery or chemotherapy is indicative of success of treatment. For example, in patients with non-metastatic lung cancers, a subset is cured after curative-intent first line therapy . Current routine clinical surveillance involves serial radiographic imaging, however, this method can only detect macroscopic disease recurrence and is frequently inconclusive (Kocak et al 2005; Huang et al 2012). Unfortunately, outcomes are poor after clinical disease progression (Hung et al 2009). Detection of minimal residual disease (MRD) for solid tumors provides physicians with an opportunity to adjust treatment before macroscopic recurrence or clinical relapse (Chaudhuri et al 2017) (**Figure 1**). For example, patients with MRD might be directed to adjuvant chemotherapy, whereas patients without MRD could be monitored instead of overtreated.

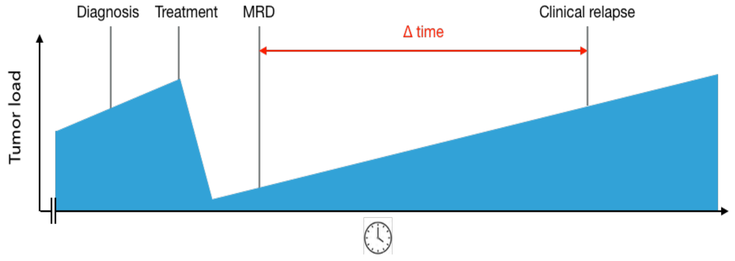


Figure 1. Bespoke MRD Assay clinical benefit. Detection of MRD provides a physician with an opportunity to evaluate alternative treatment options ahead of clinical relapse.

ELIGIBILITY AND PROTOCOL

The study will enroll 500 patients across three cohorts. Patients must be older than 18 with surgical resection planned for stage II or IIIA NSCLC. There are three cohorts:

- **Cohort #1: Neoadjuvant Therapy** – enrollment prior to initiation of treatment based on radiographic staging
- **Cohort #2: Pre-Surgery** – enrollment within 30 days of planned surgery, based on surgical pathology
- **Cohort #3: Post-Surgery** - enrollment occurs prior to adjuvant therapy, based on surgical pathology.

We will conduct an initial evaluation of ctDNA results after enrollment of 100 eligible patients. All patients will be followed for survival and recurrence for a maximum of 60 months from the date of surgery. The primary objective is to correlate the presence of ctDNA following complete surgical resection with disease-free survival. Secondary objectives are to evaluate the changes in ctDNA after complete resection at pre-specified intervals and correlate the presence of ctDNA with overall survival.

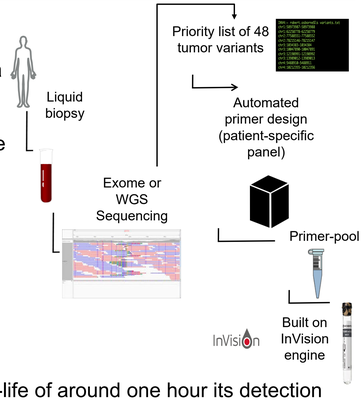
STUDY SCHEMA

Study Phase	***Baseline***			***Pre-Surgery***	***Surgery***	***Trial Period***					
Visit	Cohort #1[1]	Cohort #2[3]	Cohort #3[4]	Cohort #1[2]	Tx	PO V1[10]	PO V2[6, 10]	V3[6]	V4 – 11[6]	V12[6]	PD[6,7]
Day/Week	Pre-neoadjuvant treatment	-30d surgery	Pre-adjuvant treatment		0d	48-72h	4-6w	6m	12m	5y EoS	0-5y
Informed consent	X	X	X								
Demographics and Medical History	X	X	X								
Surgical Resection[9]					X[9]						
Tissue Storage[5]					X[5]						
Clinical Status	X[1]	X[3]	X[4]	X[2]		X	X[10]	X	X	X	X
Inivata ctDNA[8]	X[1]	X[3]	X[4]	X[2]		X	X[10]	X	X	X	X[6,7]
CRFs	X[1]	X[3]	X[4]	X[2]		X	X[10]	X	X	X	X

[1] Cohort #1 subjects receiving neoadjuvant therapy will have a baseline visit prior to the initiation of neo-adjuvant therapy. [2] Cohort #1 subjects receiving neoadjuvant therapy will have an additional pre-surgery blood draw with clinical status assessment and CRF completion collected after the completion of neoadjuvant therapy and any time prior to surgery. [3] Cohort #2 subjects will have a baseline visit occurs up to 30 days prior to surgery. [4] Cohort #3 subjects will have a baseline visit post-operatively and prior to adjuvant therapy; but no more than 2 months post-operatively. [5] Tissue Storage: All enrolled subjects will submit FFPE (block or slides or sections) to ALCMI Biorepository. [6] Visit may occur within +/- 2 weeks of stated timepoint. [7] PD (Progressive disease): An additional blood collection will occur at the time of relapse, if it occurs outside of scheduled study visits. [8] Inivata ctDNA (liquid biopsy): 30mL of blood will be collected and shipped immediately to Inivata. [9] All subjects will have surgery either prior to (Cohort #3) or during study participation (Cohorts 1 and 2). [10] Cohorts 1 and 2 only.

ASSAY

The assay begins with a list of tumor variants and associated variant allele fractions (VAFs). The VAF is the fraction of molecules of DNA at a particular locus that contain the variant. The list of tumor variants derives from next-generation sequencing (NGS) of the initial liquid biopsy. The tumor variants and associated VAFs are input into a proprietary algorithm which outputs a multiplex PCR design that targets up to 48 variants. The multiplex PCR assay is performed on cell-free DNA isolated from a patient's peripheral blood sample taken at a time point of interest. Proprietary algorithms are used to analyse the resulting sequencing data and determine whether circulating tumor DNA is detected. As circulating tumor DNA has a half-life of around one hour its detection gives real-time assessment on whether residual tumor remains (Wan et al 2017).



STUDY SITES

The study is currently open at the following sites and additional sites are being actively recruited:

- Orange Coast Memorial Medical Center, Fountain Valley, California
- Saddleback Memorial Medical Center, Laguna Hills, California
- Long Beach Memorial Medical Center, Long Beach, California
- Northside Hospital, Atlanta, Georgia
- Rush University Medical Center, Chicago, Illinois
- Dana Farber Cancer Institute, Boston Massachusetts (Pending)
- Saint Louis Cancer Care, Bridgeton, Missouri
- Washington University School of Medicine, St. Louis, Missouri
- Vanderbilt University Medical Center, Nashville, Tennessee
- Baptist Memorial Hospital, Memphis, Tennessee

STUDY CONTACTS

For interested sites, contact: Richard Erwin (284) 444-2181 rerwin@alcmi.net
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