ctDNA Dynamics in Early Stage Node Negative Non-small Cell Lung Cancers

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Abstract #3387

Introduction

Patients with early-stage non small cell lung cancers (NSCLC) have a high risk of relapse and death even after curative intent surgery[1]. Detection of circulating tumour DNA (ctDNA) in plasma perioperatively is associated with shorter recurrence free survival (RFS) and overall survival (OS)[2-4].

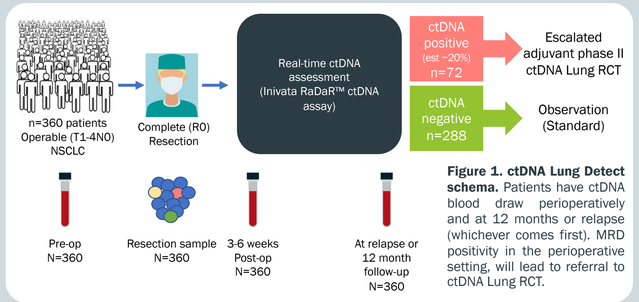

Figure 1. ctDNA Lung Detect schema. Patients have ctDNA blood draw perioperatively and at 12 months or relapse (whichever comes first). MRD positivity in the perioperative setting, will lead to referral to ctDNA Lung RCT.

ctDNA Lung Detect (Fig. 1, NCT05254782) is an investigator-initiated prospective study of ctDNA detection and association with RFS in patients with clinical stage I NSCLC.

<u>The objective is to identify node negative lung cancer patients at high risk of relapse after surgery using ctDNA.</u> Patients with detectable ctDNA are enrolled into ctDNA Lung RCT (NCT04966663) randomizing patients to adjuvant chemoimmunotherapy vs observation. The primary study endpoint for ctDNA Lung Detect is determining rate of detection of ctDNA in perioperative samples in patients with T1-2 and multifocal T3-4 (<4 cm) N0 NSCLC patients. Secondary endpoints include exploring associations between ctDNA kinetics/status with RFS and OS.

Methods

Patients with clinically staged T<4cm N0 NSCLC planned for surgical resection at the Princess Margaret/University Health Network (Toronto ON, Canada) underwent ctDNA assessment before and after surgery (~1 month, and 1 year). ctDNA minimal residual disease was detected using the highly sensitive and specific tumor-informed Residual Disease and Recurrence (RaDaR™, NeoGenomics Ltd, Cambridge, UK) assay (Fig. 2). This assay can track up to 48 cancer-tissue specific specific variants in plasma samples with a limit of detection of 0.0011% variant allele frequency (VAF)[2].

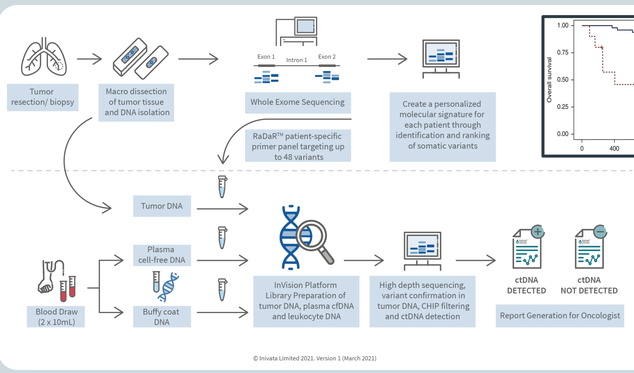

Figure 2. RaDaR™ assay technology. Patients with positive ctDNA at the landmark time point (2 weeks to 4 months after treatment) had a shorter OS. Inset image adapted from Gale et al. (2022). Image supplied by Inivata.

Results

As of Feb 17, 2023, 70 patients have results (Fig. 3). Median age is 71 years (51-85). Median pathologic tumor size is 20.5mm (2-60); a total of 12 patients had primaries >40mm. Tumor sizes for ctDNA positive was 26mm (13-60) vs ctDNA negative 19mm (2-47), p = 0.006. Patient and cancer details are in Fig 4.

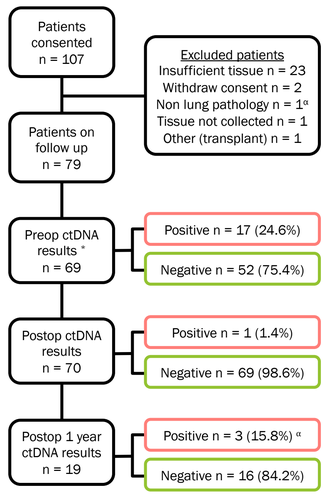

Figure 3. Patient flow diagram (above).
[a] This patient was positive perioperatively, and excluded after surgical resection
* One patient did not have preoperative blood work

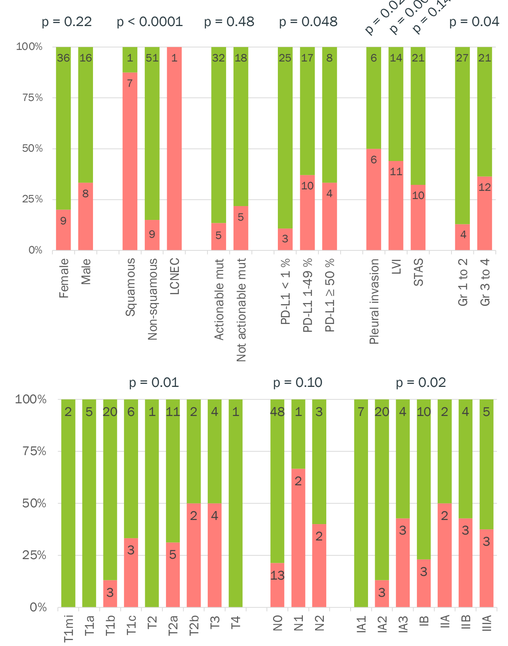

Figure 4. Patient demographics and cancer characteristics (right).

ctDNA negative (n) ctDNA positive (n)

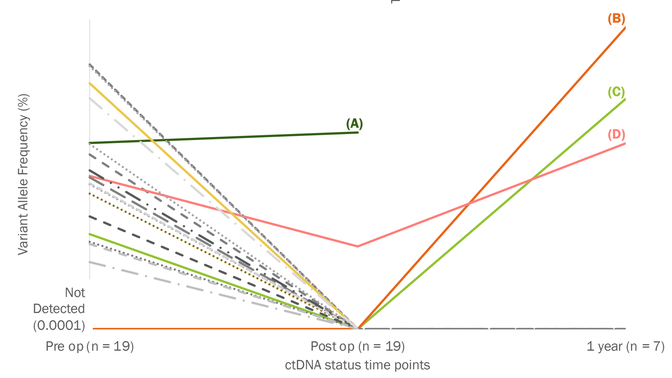

Figure 5. ctDNA dynamics in patients with at least one positive ctDNA result at any time point. VAF is shown for individual patients. Only 7 have 1 year followup results available. **(A)** Resected lung nodule, found to be non-lung pathology (excluded). **(B)** Perioperative ctDNA negative presenting with metastatic disease on surveillance CT. **(C)** Cleared ctDNA with surgery and asymptomatic recurrence detected by ctDNA positivity prompting CT imaging. **(D)** T3N2 disease w/ persistent ctDNA positivity despite ongoing adjuvant treatment.

Discussion/Conclusions

- To our knowledge, this study will be one of the largest cohorts of stage I resected NSCLC patients with ctDNA profiling. Using the tumor informed RaDaR™ assay, we report preoperative ctDNA detection in 24.6% of cases, a similar rate to other series.
- Tissue requirements for pathology constrain tumor-based panel development in small cancers. Approximately 21% of cases had insufficient tissue for personalized assay development.
- Integration into real world diagnostic pathways will be important as technology develops to allow personalized assays to be constructed from biopsy specimens. Decreasing turn around time required for panel development will improve integration into routine clinical care.

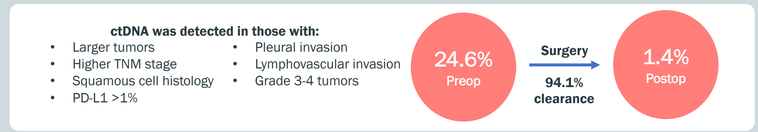

Figure 6. ctDNA detection and clearance in the perioperative setting.

- The postoperative positivity rate is 1.4%, which is lower than expected. Only one patient (Fig 5 patient D) was positive postoperatively. This patient was upstaged with T3N2 disease treated with adjuvant chemotherapy and is now on adjuvant targeted therapy. ctDNA positivity persists at 1 year without radiographic or clinical evidence of recurrence.
- 2 patients have recurred, 1 each in preoperative ctDNA negative and positive (Fig 5 patient B and C, respectively).
- Detecting micrometastatic disease with a reliable assay to select patients for adjuvant therapy remains challenging. Standard of care for T <4cm is observation but recurrence is high[1,5].
- Our results support ongoing testing beyond the initial MRD landmark in patients with surgically resected disease, thus we are adding a 6 month collection time point for later analysis. Assessment of the impact on RFS in clinical stage I NSCLC post resection is ongoing.

References

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In patients with resected clinical stage I NSCLC, approximately 25% have detectable ctDNA pre-operatively with surgical clearance in over 94% of cases.

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