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# Clinical validation and utility of InVision ctDNA in advanced non-small cell lung cancer (NSCLC) patients


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## INTRODUCTION

- Circulating tumor DNA (ctDNA) can be used for somatic mutation detection, such as *EGFR*, *BRAF* or *KRAS* mutations as well as fusions (ALK and ROS1), in NSCLC patients
- Comprehensive molecular profiling using liquid biopsy ctDNA is rapidly gaining traction in routine clinical practice
- However, there has been variable degree of accuracy and performance published to date
- Also, there is a lack of prospective data on clinical outcomes for patients with actionable genomic alterations in liquid biopsy
- Here, we describe the clinical validation and utility of the InVision platform (InvisionFirst™-Lung, InvisionSeq™-Lung) in a large prospective cohort of advanced NSCLC patients

## METHODS

- We performed a prospective, single-centre, observational study enrolling advanced NSCLC patients including treatment-naïve, on TKI treatment or at progression to targeted therapy
- ctDNA molecular analysis was performed using amplicon-based NGS (InVision platform) and where available, in tissue by Sanger sequencing or a sensitive validated allele-specific technique
- Clinical validation was performed for core gene variants of EGFR Exons 18-21, BRAF V600, MET Exon 14, ERBB2 Ins 20, ALK & ROS1 fusions, KRAS and STK11, according to clinical practice guidelines[1-3]
- Patients treated with matched targeted therapies evaluable for disease control at 3 months, according to RECIST1.1 criteria by Investigator, were collated for outcome analyses

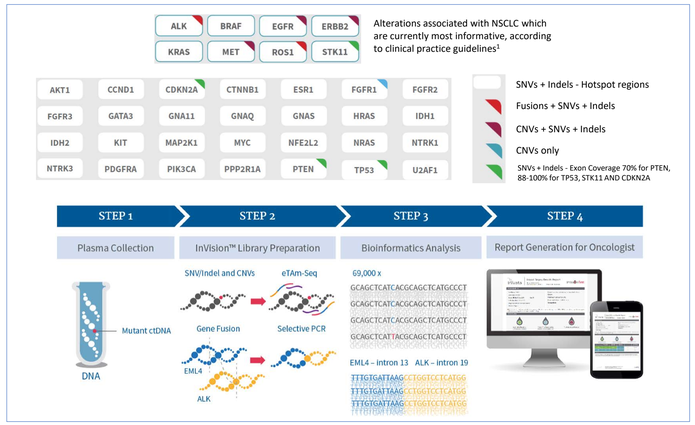


***Figure 1.*** The InVisionFirst™-Lung assay identifies SNVs, indels, CNVs and gene fusions with whole gene and gene hotspots, using an amplicon-based technology to selectively amplify genomic breakpoints. The sequence of the junctions are then identified using NGS, allowing the genomic breakpoint in ctDNA to be mapped[4]

## RESULTS

- 362 advanced NSCLC patients recruited
  - 172 treatment-naïve
  - 190 were pre-treated patients with known tissue molecular profile (EGFR, BRAF, ALK, ROS1, MET)

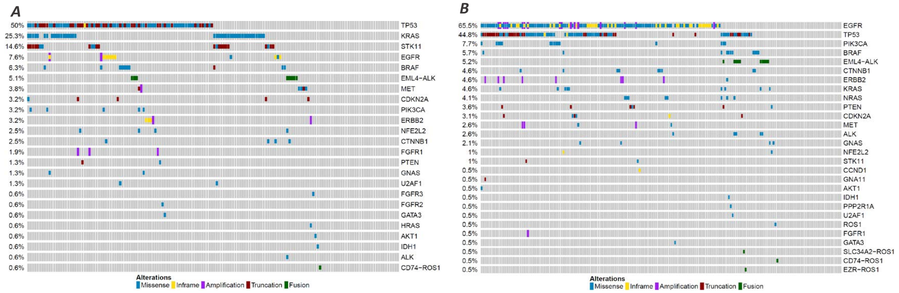


***Figure 2A & B:*** Invision liquid biopsy comprehensive genomic profiles of (A) treatment-naïve and (B) pre-treated patients

- For clinically-relevant gene variants, concordance agreement was 94% where ctDNA and tumor tissue analysis was available, with 76% sensitivity and 97% specificity

| Key gene variants | Tissue and Liquid | Tissue only | Liquid only | No call | PPV | NPV | Sensitivity | Specificity | Concordance |
|---|---|---|---|---|---|---|---|---|---|
| EGFR Exons18-21 | 7 | 1 | 1 | 78 | 77.8 | 98.8 | 87.5 (0.473-0.997) | 98.7 (0.931-1.00) | 97.7 (0.919-0.997) |
| EML4-ALK fusion | 8 | 5 | NA | NA | - | - | 61.5 (0.316-0.861 | - | - |
| ROS1 fusion | 1 | 1 | NA | NA | - | - | 50.0 (0.126-).987) | - | - |
| BRAF V600E | 2 | 1 | 0 | 75 | 100.0 | 98.68 | 66.7 (0.094-0.992) | 100 (0.952-1.00) | 98.7 (0.931-0.999) |
| ERBB2 Exon 20 | 2 | 0 | 0 | 49 | 100.0 | 100.0 | 100.0 (0.158-1.00) | 100.0 (0.927-1) | 100.0 (0.930-1) |
| MET Exon14 | 1 | 2 | 0 | 45 | 100.0 | 95.8 | 33.3 (0.008-0.906) | 100.0 (0.921-1.00) | 95.8 (0.875-0.995) |
| KRAS | 22 | 3 | 7 | 56 | 75.9 | 95.0 | 88.0 (0.688-0.975) | 88.9 (0.784-0.954) | 88.64 (0.801-0.944) |
| STK11 | 2 | 1 | 1 | 17 | 66.7 | 94.4 | 66.7 (0.094-0.992) | 94.4 (0.727-0.999) | 90.5 (0.696-0.988) |
| **Core gene variants** | 45 | 14 | 9 | 320 | 83.3 | 95.8 | 76.3 (0.634-0.864) | 97.3 (0.949-0.987) | 94.1 (0.912-0.962) |
| **Overall panel** | 65 | 27 | 36 | 1078 | 64.4 | 97.6 | **70.7 (0.602-0.797)** | **96.8 (0.956-0.977)** | **94.8 (0.934-0.960)** |

***Table 1*** Statistical summary of clinical validation (concordance, sensitivity and specificity analyses) for InVision platform by clinically relevant core gene variants and overall panel, as compared to tissue molecular analysis.

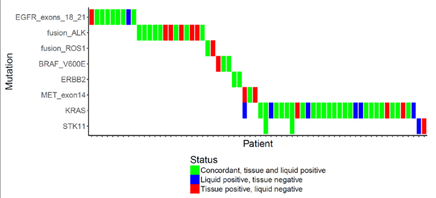


***Figure 2.*** Concordance of amplicon-based assay for liquid biopsy compared to tissue biopsy analysis

- 58 patients were evaluable for outcome analysis
  - 89% had disease control at 3 months of therapy
  - Response rate at 3 months was 61%
  - Median progression free survival was 5.7 months

| Prior therapy for advanced disease | Genomic alteration | N | Number still on targeted therapy at 3 months | % still on targeted therapy at 3 months |
|---|---|---|---|---|
| Untreated for advanced disease | **All** | 3 | 3 | 100% |
| | EGFR mutation | 1 | 1 | 100% |
| | Braf v600 mutation | 1 | 1 | 100% |
| | ALK / ROS1 fusion | 1 | 1 | 100% |
| Prior cytotoxic chemotherapy for advanced disease but no targeted therapy | **All** | 10 | 9 | 90% |
| | EGFR mutation | 0 | 0 | - |
| | Braf v600 mutation | 2 | 1 | 50% |
| | ALK / ROS1 fusion | 7 | 7 | 100% |
| | MET Exon 14 | 1 | 1 | 100% |
| Prior therapy with targeted therapy | **All** | 45 | 40 | 89% |
| | EGFR mutation (with T790M) | 36 | 32 | 88% |
| | Braf v600 mutation | 2 | 1 | 50% |
| | ALK / ROS1 fusion | 7 | 7 | 100% |
| **Overall** | | 58 | 52 | 89% |

***Table 2.*** Summary of Results: Breakdown of patients by disease setting and by genomic alteration along with their 3-month disease control rate.

## CONCLUSION

- Our data endorses ctDNA molecular profiling using InVision as an accurate and reliable tool for the detection of clinically relevant molecular alterations in advanced NSCLC patients
- Clinical outcomes in patients who have been treated with targeted therapy based on actionable alterations detected by amplicon-based NGS ctDNA analysis by InVisionFirst-Lung and InVisionSeq-Lung are consistent with those reported based on tissue profiling

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References:
[1]Novello S, Barlesi F, Califano R, et al. Ann Oncol Off J Eur Soc Med Oncol 27:v1–v27, 2016
[2]Kalemkerian GP, Narula N, Kennedy EB, et al. J Clin Oncol Off J Am Soc Clin Oncol 36:911–919, 2018
[3]NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer
[4]Plagnol V , Woodhouse S, Howarth K, Lensing S, Smith M, Epstein M, et al. PLoS ONE (2018) 13(3): e0193802 doi.org/10.1371/journal. pone.0193802