# Concurrent DNA and RNA NGS Testing to Characterize Rare Fusions in Advanced NSCLC Patients

J.L. Feliciano[1], L. Gai[2], Z. Rivers[2], A.J. Hockenberry[2], H. Nimeiri[2], K.A. Beauchamp[2], R. Ben-Shachar[2], J. Guinney[2], and J.D. Patel[3]

[1]Johns Hopkins University School of Medicine, Baltimore/MD/USA ,[2]Tempus AI, Inc., Chicago/IL/USA ,[3]Northwestern University Feinberg School of Medicine, Chicago/IL/USA

2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024
SAN DIEGO, CA USA

## INTRODUCTION

Therapy directed at molecular actionable variants improves survival in patients with advanced NSCLC and is standard of care. Although there is familiarity with common fusion targets such as *ALK*, *ROS1*, and *RET*, there is growing evidence that emerging rare fusion targets (eSVs) in advanced NSCLC may be promising targets for matched therapies that also may lead to improved outcomes. Here we report the prevalence of rare *BRAF*, *NRG1*, and *EGFR* fusions, and their co-occurrence with other NCCN recommended actionable NSCLC targets, using concurrent DNA-RNA NGS testing in a real-world patient cohort.

## METHODS

Deidentified records were extracted from the Tempus multimodal database, consisting of 5,570 advanced (Stage IIIB-IV) patients with a primary diagnosis of adenocarcinoma NSCLC who underwent solid-tumor testing with both DNA-seq and RNA-seq (Tempus xT and xR assays, respectively). Concurrent RNA-NGS and DNA-NGS pipelines were run separately and manually reviewed as part of the Tempus clinical workflow. NCCN recommended testing for targeted variants assessed in co-mutational analyses included ALK, RET, ROS1, and NTRK1/2/3 fusions, MET exon 14 skipping variants, EGFR pathogenic single nucleotide variants (SNVs)/indels (e.g., exon 19 deletions), BRAF V600E, and KRAS G12C.

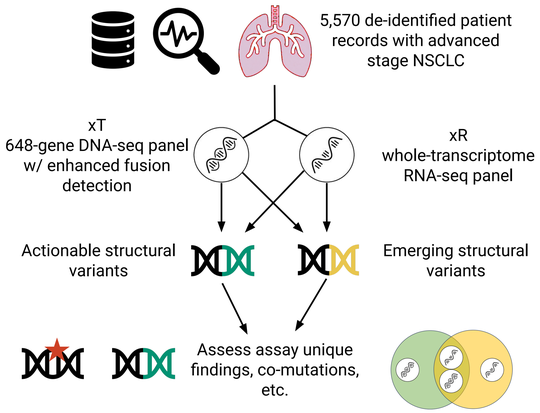


**Figure 1.** Schematic overview of study design.

## SUMMARY

- Concurrent DNA-RNA NGS doubled the number of emerging rare fusion variants detected in advanced NSCLC patients compared to DNA-NGS alone.
- 50% of BRAF fusions were noted in patients with classic EGFR activating mutations who had received prior TKI and may represent a distinct, and potentially targetable, acquired resistance mechanism.

## RESULTS

| | Overall (n=5570) | eSV-Negative (n=5537) | eSV-Positive (n=33) | P-value |
|---|---|---|---|---|
| **Tissue site, N (%)** | | | | |
| Primary tumor | 3863 (69.4) | 3843 (69.4) | 20 (60.6) | 0.2 |
| Metastasis | 1640 (29.4) | 1628 (29.4) | 12 (36.4) | |
| Unknown | 67 (1.2) | 66 (1.2) | 1 (3.0) | |
| **Cancer Stage, N (%)** | | | | |
| Stage 3B | 324 (5.8) | 323 (5.8) | 1 (3.0) | 0.9 |
| Stage 3C | 91 (1.6) | 91 (1.6) | 0 (0) | |
| Stage 4 | 5089 (91.4) | 5057 (91.3) | 32 (97.0) | |
| Other | 42 (0.8) | 42 (0.8) | 0 (0) | |
| Unknown | 24 (0.4) | 24 (0.4) | 0 (0) | |
| **Smoking Status, N (%)** | | | | |
| Current or Former Smoker | 3925 (70.5) | 3913 (70.7) | 12 (36.4) | <0.001 |
| Non-Smoker | 962 (17.3) | 945 (17.1) | 17 (51.5) | |
| Unknown | 683 (12.3) | 679 (12.3) | 4 (12.1) | |
| **Sex, N (%)** | | | | |
| Female | 2989 (53.7) | 2969 (53.6) | 20 (60.6) | 0.5 |
| Male | 2581 (46.3) | 2568 (46.4) | 13 (39.4) | |
| **Age at tissue collection, median [25%,75%]** | 67.8 [61.3,75.4] | 67.8 [61.3,75.4] | 70.4 [61.5,79.0] | 0.5 |
| **Race, N (%)** | | | | |
| American Indian or Alaska Native | 7 (0.1) | 7 (0.1) | 0 (0) | 0.03 |
| Asian | 201 (3.6) | 201 (3.6) | 0 (0) | |
| Black or African American | 462 (8.3) | 462 (8.3) | 0 (0) | |
| Native Hawaiian or Other Pacific Islander | 3 (0.1) | 3 (0.1) | 0 (0) | |
| Other Race | 214 (3.8) | 211 (3.8) | 3 (9.1) | |
| Unknown | 1847 (33.2) | 1829 (33.0) | 18 (54.5) | |
| White | 2836 (50.9) | 2824 (51.0) | 12 (36.4) | |
| **Ethnicity, N (%)** | | | | |
| Hispanic or Latino | 171 (3.1) | 171 (3.1) | 0 (0) | 0.3 |
| Not Hispanic or Latino | 2434 (43.7) | 2423 (43.8) | 11 (33.3) | |
| Unknown | 2965 (53.2) | 2943 (53.2) | 22 (66.7) | |

**Table 1.** Demographics and clinical characteristics.

### eSV prevalences vary among NSCLC patients

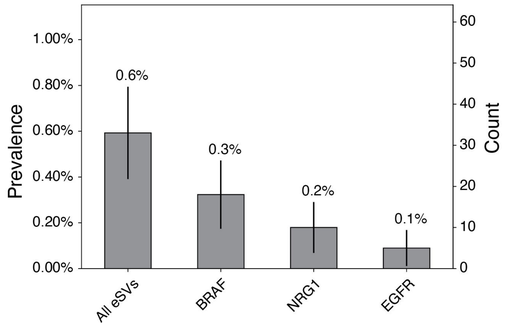


**Figure 2.** Prevalence (left axis) and counts (right axis) of indicated eSV (including all, at left) within the study cohort.

### *BRAF* fusions tend to co-occur with actionable *EGFR* variants

| Fusion gene | n | Patients w/ NCCN-recommended targeted mutations | *EGFR* Exon 19 Del | EGFR T790M | *KRAS G12C* |
|---|---|---|---|---|---|
| *BRAF* | 18 | 9 (50%) | 9 | 2* | 0 |
| *NRG1* | 10 | 1 (10%) | 0 | 0 | 1 |
| *EGFR* | 5 | 0 (0%) | 0 | 0 | 0 |

**Figure 3.** Counts of actionable co-mutations for the studied eSVs. *note that both of the observed T90M mutations were observed in exon 19 deletion backgrounds.

### Concurrent DNA-NGS and RNA-NGS increases eSV detection

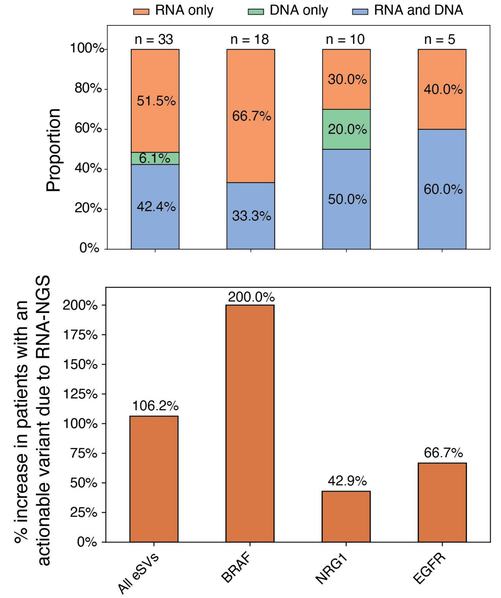


**Figure 4.** Concordance (blue) and assay unique (green, orange) fusions detected by DNA- and RNA-NGS (top). Percent increase in patients with an identified eSV relative to DNA-NGS only (bottom).

**Correspondence:** justin.guinney@tempus.com