Building an effective concordance study: Plasma Next Generation Sequencing (NGS) for oncogenic fusion detection in non-small cell lung carcinoma (NSCLC)

**Background**
- NSCLC patients at Dana-Farber Cancer Institute were sequenced for ALK/ROS1/NTRK fusions to identify fusion-positive patients in tumor who had undergone plasma NGS by Guardant360.
- A separate tube of plasma from consented patients was analyzed using ctDx-Lung.
- Researchers involved in specimen and data handling were blinded until results were locked.
- Unblinded cases were available for ad hoc analysis.

**Study Cohort**
168 patients were found to have had clinical Guardant testing and to have consented to research. 28 patients had tumor testing positive for an ALK, ROS1, or RET rearrangement. 12 patients were excluded as there was no adequate plasma for analysis.

**Results**

**Reported Fusions**
- ctDx-Lung detected 13 cases and tended to report higher AF % in fusions than Guardant360, which detected 7 cases.
- Circulating tumor DNA (indicated by 7PS3 SNVs) was detected in discordant cases.

**Breakpoint Schematics**
- Fusion breakpoints detected are heterogeneous.
- ctDx-Lung reports more out-of-frame/inverted fusion variants than Guardant360.

**Technical Considerations**
- Fusion partner and oncogenic breakpoints in NSCLC are often unpredictable.
- cFlux360 and ctDx-Lung2 cFlux different bait/probe lengths which may impact target fragment capture efficiency.

**Conclusions**
- Rigorous evaluation of plasma NGS assays against a tumor standard is needed to effectively identify actionable mutations in more patients for improved treatment and clinical trial enrollment.

**References**
2. Papadimitrakopoulou, V. Proceedings: AACR Annual Meeting 2019; Atlanta, GA.

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