Background

- **KRAS gene** mutated in about 30% non-small cell lung cancer (NSCLC). Immune checkpoint inhibitors (ICIs) have been applied widely and KRAS mutations were considered to be related to superior clinical response. However, several studies revealed that co-mutated driver genes such as TP53, STK11 would impact the therapy effects. G12 is the most frequent KRAS mutated dot in NSCLC. The co-mutational status with driver genes in different G12 subtypes have not been fully explored.

Methods

- 903 cases of Chinese NSCLC patients were included in our analysis. Immunohistochemistry and 381-gene panel next-generation sequencing (NGS) testing had been performed in their tumor tissue specimen. PD-L1 expression level was evaluated by the tumor positive score (TPS). Tumor mutational burden and MSI status were evaluated via NGS testing.

Results

- G12C/D/V/A/R/S/F/L/I/Y were detected but only G12C/D/V/A showed mutational rates above 5%. The number of cases were 294 (32.6%), 143 (15.8%), 157 (17.4%), 81 (9%) in G12C/D/V/A, separately. These four G12 subtypes were basically mutually exclusively, except 52 cases (6%) had 2 or 3 subtypes. The mutational rates of G12C/D/V/A in TP53, LRP1B, STK11 and KEAP1-mutated patients were balanced, with the G12C were co-occurred most in KEAP1-mutated group (58.2%), G12D were co-occurred most in STK11-mutated group (19.6%) (Figure 1).

- Compared to other KRAS-mutated cases, G12-mutated had similar TMB levels (Figure 2). In 546 cases with TPS data, 62% in G12C-mutated group were TPS>1% while only 45% in G12V-mutated group were TPS>1% (Figure 3).

- According to the TCGA NSCLC cohort, there was no significant difference in overall survival between these subtypes, whether co-mutated with TP53/LRP1B/STK11/KEAP1 or not (Figure 4).

Conclusion

- In Chinese NSCLC, the main KRAS G12 subtypes were G12C/D/V/A and G12C was the most frequent. KRAS G12C-mutated NSCLC were most probable to co-mutated with KEAP1 gene, and have relative high PD-L1 expression. G12C/D/V/A had little effect on TMB, and had no effect on OS of early lung cancer.