Efficacy of immune checkpoint inhibition in RET fusion-positive non-small cell lung cancer patients

Sireci AN,1 Morosini D,1 Rothenberg SM1
1Loxo Oncology Inc., Stamford, CT, USA

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Background

- Immune checkpoint inhibitors (ICIs) are approved for the treatment of advanced non-small-cell lung cancer (NSCLC).
- RET fusions occur in 1-2% of NSCLCs and affected patients may benefit from selective RET inhibition with investigational RET targeted agents such as LOXO-292 (perluzumab) and BLU-667 (pralsetinib).1-3
- RET fusion-positive tumors have been shown in retrospective studies to have poor response to the pembrolizumab treatment setting.1-3
- Additionally, in the KEYNOTE-189 study examining the efficacy of the ICI pembrolizumab in combination with platinum and pemetrexed, patients with RET fusion-positive NSCLC were not specifically identified or excluded (unlike patients with EGFR or ALK alterations).4 Therefore, the efficacy of the regimen in patients with RET fusion-positive NSCLC is unknown.
- Databases combining tumor genotypic information with data on therapeutics and outcomes provide a valuable source for large-scale, real-world evidence generation.

Methods

- Data from patients with RET fusion-positive advanced NSCLC were mined from two large databases: the Guardant Health Database and the Flatiron Health Clinicogenomics Database.

Guardant Health Database

- Patients with tumors harboring an in-frame RET fusion were identified using the Guardant Health Database, which includes results from over 100,000 circulating tumor DNA samples analyzed using the Guardant360 assay:
  - This assay detects single-nucleotide variants (SNVs) and small insertions or deletions (indels) in 74 genes, copy number alterations in 19 genes, and fusions in 6 genes.6
  - Results from individuals with a diagnosis of advanced (stage IIIb or IV) lung adenocarcinoma or NSCLC not otherwise specified (NOS) with an activating RET fusion detected by clinical Guardant360 testing between January 2016 and March 2019 were extracted.
  - Using a three-way, FDA-compliant data linkage platform, molecular testing results from Guardant Health were then linked to clinical information from Komodo Health’s Healthcare Map, which consists of longitudinal data from more than 300 million US patients.

Flatiron Health Clinicogenomics Database

- This database links clinical data from electronic health records from Flatiron Health’s network across the US with genomic data from Flatiron’s Foundation Medicine Cancer Genomics Platform testing.
- Flatiron’s longitudinal, demographically and geographically diverse database contains electronic health record (EHR) data from over 256 cancer clinics (~400 sites of care) including more than 2 million active US cancer patients. The database includes advanced/metastatic NSCLC cohort data from more than 55,000 patients diagnosed since January 1, 2015.

Results

- A total of 64 patients met eligibility criteria and were included in this study (n=42 from Guardant360; n=22 from Flatiron), Figure 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Flatiron Clinicogenomics Database (n=42)</th>
<th>Guardant360 Database (n=42)</th>
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<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>61.6 (9.6)</td>
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<tr>
<td>Received systemic therapy</td>
<td>100%</td>
</tr>
<tr>
<td>Time to treatment discontinuation</td>
<td>not reported in caves</td>
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Conclusions

- RET fusions were found in 1-2% of NSCLCs in the Flatiron dataset, consistent with known epidemiology. The lower prevalence in the Guardant360 dataset may be explained by known limitations in the sensitivity of liquid biopsy in fusion detection and biologic variability in cell free DNA shedding in NSCLC.
- When ICIs were used in the first-line setting, they were used predominantly with platinum chemotherapy and pemetrexed, the regimen used in KEYNOTE-189.
- Median time on treatment for first-line RET+ NSCLC using ICI was 5.8 months (median 1day; max=21.6 months) with 48% of patients remaining on therapy at 6 months.
- This is comparable with time of exposure for KEYNOTE-189 (median 7.2 months; min=1 day; max=20.1 months), 66% remaining on therapy at 6 months.6
- Although the overall numbers of patients are small, these data indicate the potential for concurrent with single-agent ICIs in the second, or later-line setting.
- RET fusions in NSCLC are not predictive for more favorable responses to standard treatment with first-line ICI-containing treatment regimens.

Limitations

- Estimates of mean duration of therapy are derived from data from multiple ICI-containing regimens not limited to KEYNOTE-189. This limits the comparison to the KEYNOTE-189 study, which was performed with a single regimen.
- 16% of patients with tumor RET fusions were excluded from this analysis due to co-occurring pathogenic EGFR, ALK and ROST mutations in the Flatiron dataset and EGFR mutations in the Guardant360 dataset; other coexisting mutations were not an exclusion criterion in this study, but represented a low proportion of the population (e.g. KMTS, mES, BRAF, n=13; ALK, n=3 of the complete 90-patient sample from Guardant360, 1 patient had a BRAF mutation in the eligible 39-patient cohort from Flatiron).
- The rate of concurrent EGFR mutations in the Guardant360 dataset is higher than expected and requires additional investigation.

References

9. KEYTRUDA (pembrolizumab) Package Insert, Merck. 2019

Acknowledgements

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Figure 1. Patient cohorts

- RET patients with NSCLC
- ORL patients with NSCLC
- Other ICI containing combination regimens

Figure 1a. Flatiron patient cohort

- SMAD with advanced NSCLC
- ORL with advanced NSCLC
- Patients with aggressive RET fusions

Figure 1b. Guardant360 patient cohort

- RET-KIF5B fusion
- RET-MET fusion
- RET-ALK fusion

Figure 2. Treatment regimens by line of therapy: all patients

Figure 3. Kaplan-Meier analysis of time to treatment discontinuation

*In patients with concurrent actionable co-mutants with RET fusion-positive status by line of therapy, all patients. ICI, immune checkpoint inhibitor.