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

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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 (selpercatinib) and BLU-667 (pralsetinib).[1-3]
- *RET* fusion-positive tumors have been shown in retrospective studies to have poor response to ICI monotherapy in the second-line setting.[4,5]
- 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).[6] 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.
- We mined two large oncology databases for *RET* fusion-positive advanced NSCLC cases and examined time on therapy with ICIs (both in monotherapy and in combination) as a surrogate for efficacy in patients with *RET* fusion-positive tumors. Duration of therapy in the first-line setting was compared to published data for KEYNOTE-189.

Methods

- Data from patients with *RET* fusion-positive advanced NSCLC were mined from two large databases: the Guardant Health Database and the Flatiron Health Clinico-Genomics 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[7,8]
  - 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 third-party HIPAA-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 Clinico-Genomics Database

- This database links clinical data from electronic health records from Flatiron Health's network across the US with genomic data from Foundation Medicine Cancer Genomics Platform testing:
  - Flatiron Health's longitudinal, demographically and geographically diverse database contains electronic health record (EHR) data from over 265 cancer clinics (~800 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, 2011

Eligibility criteria

- Diagnosis of advanced/metastatic NSCLC.
- Age 18 or older at time of diagnosis.
- Confirmed *RET* fusion via Guardant360 or Foundation One testing.
- No co-occurring *EGFR* mutations.
- Received systemic therapy for the advanced/metastatic NSCLC.

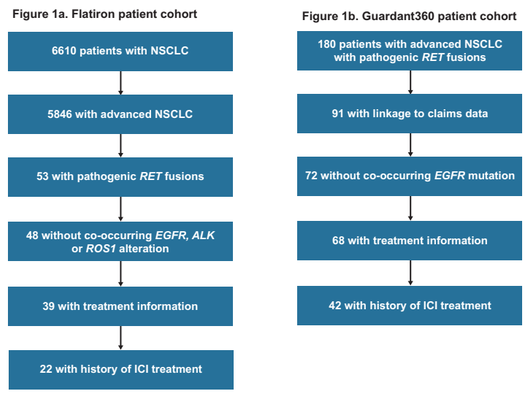
Statistical analysis

- Baseline characteristics were described at the time of the advanced/metastatic diagnosis (index date).
- Treatment sequencing was described by line of therapy.
- Patients could not be definitively stated to have discontinued therapy if their last anti-cancer therapy occurred within 60 days of the end of the database and were assumed to still be on treatment for duration of therapy analyses.
- Time-to-event analyses were conducted using the Kaplan-Meier method (overall and progression-free survival and time to treatment discontinuation).
- Analyses were performed with SAS Enterprise Guide 7.1.5. Statistical significance was accepted at the P <0.05 level (two-sided test).

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**.

Figure 1. Patient cohorts



ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer.

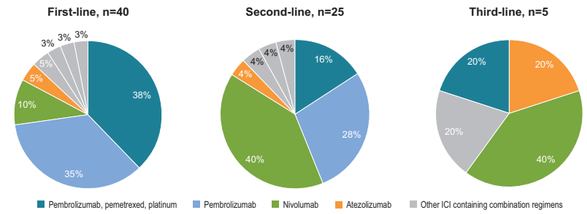
- Baseline characteristics are summarized in **Table 1**.
- Treatment patterns demonstrated use of a variety of ICIs in both combination and monotherapy across lines of therapy (**Figure 2**):
  - The most common ICI-based regimens included pemetrexed + platinum + pembrolizumab (Keynote-189 regimen; first-line) and single-agent nivolumab (second-line)
- Time to treatment discontinuation (**Figure 3**):
  - First-line regimens: median 5.8 months (min=1 day, max=21.9 months), 48% of patients remained on therapy at 6 months
  - Second-line regimens: median 5.1 months (min=1 day, max=16.4 months), 46% remained on therapy at 6 months; third-line, no point estimate was made due to small sample size (n=5)

Table 1. Baseline characteristics

	Flatiron Clinico-Genomics Database (n=22)	Guardant360 Database (n=42)
Mean age, years (SD)	61.5 (9.6)	60.6 (11.4)
Female gender, n (%)	11 (50)	20 (48)
Race, n (%)		Not reported in claims
Black	1 (5)	
White	15 (68)	
Other	3 (14)	
Unknown	3 (14)	
PD-L1, n (%)		Not reported in claims
Positive	3 (14)	
Negative	4 (18)	
Unknown	15 (68)	
Stage at diagnosis, n (%)		Not reported in claims
I	1 (5)	
II	0	
III	5 (23)	
IV	16 (73)	
Non-squamous histology, n (%)	20 (91)*	Not reported in claims
Total lines of therapy, n (%)		
1	10 (45)	22 (52)
2	6 (27)	11 (26)
3	5 (23)	7 (17)
4+	1 (5)	2 (5)
RET mutation, n (%)		
C10orf118-*RET*	1 (5)	0
CCDC6-RET	3 (14)	6 (14)
GAS2-RET	1 (5)	0
KIF5B-RET	14 (64)	34 (81)
ERC1-RET	0	2 (5)
NCOA4-RET	1 (5)	0
PARD3-RET	1 (5)	0
N/A-*RET*	1 (5)	0

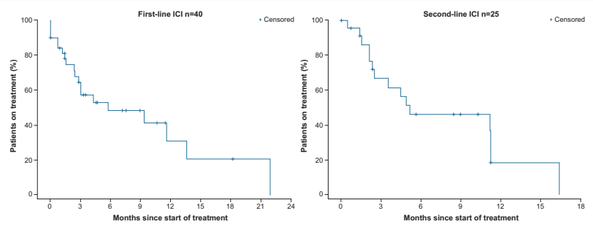
*One patient had squamous NSCLC, one patient histology not specified. SD, standard deviation; PD-L1 was recorded 15 days prior to the index diagnosis through 60 days after diagnosis.

Figure 2. ICI treatment regimens by line of therapy; all patients



*Other first-line regimens include pembrolizumab+platinum+pemetrexed+taxane (5%), pembrolizumab+platinum+pemetrexed+cabozantinib (3%), pembrolizumab+platinum+gemcitabine (3%), pembrolizumab+pemetrexed (3%). Other second-line regimens include nivolizumab+pemetrexed+taxane (4%), nivolizumab+ramucirumab+taxane (4%), pembrolizumab+pemetrexed+platinum+taxane (4%); Third-line regimens include pembrolizumab+pemetrexed (20%). ICI, immune checkpoint inhibitor.

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



*In immune checkpoint inhibitor-treated patients with *RET* fusion-positive tumors by line of therapy; all patients. ICI, immune checkpoint inhibitor.

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** (min=1 day, 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.[9]
- Although the overall numbers of patients are small, these data indicate that, consistent 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 *ROS1* 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. *KRAS*, n=8; *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.

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