Impact of *STK11* mutation on first-line immune checkpoint inhibitor outcomes in a real world *KRAS* G12C mutant lung adenocarcinoma cohort

Abstract #9106

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Background

- *KRAS*^{G12C} mutation occurs in about 14% of non-small cell lung cancer (NSCLC) patients (pts), and approximately 12% of all NSCLC pts have alterations in *STK11* gene. There is significant correlation towards co-occurrence of *KRAS* and *STK11* in lung adenocarcinoma (LUAD).[1-5]
- The introduction of KRAS G12C inhibitors into clinical trials has demonstrated promise and may provide a new therapeutic option for pts harboring *KRAS* G12C mutations.
- Immune checkpoint inhibitors (ICI) have shown benefit in LUAD pts whose cancer harbor *KRAS*^{G12C}; however, outcomes data on the impact of co-occurring *STK11* mutations are conflicting.[6,7]
- This study utilized the Guardant INFORM real-world clinical-genomic database to assess the impact of co-occurring *STK11* mutations on outcomes in pts with *KRAS* G12C mutant LUAD treated with a first-line (1L) ICI containing regimen.

Methods

Data Sources

- Guardant INFORM is a nationally representative U.S. healthcare claims clinical-genomic dataset covering over 137,000 advanced/metastatic cancer pts with reported results of circulating tumor DNA (ctDNA) test by Guardant360.[8] Over 80% are linked to treatment and procedural data. Patient's blood collection date of ctDNA tests ranges between March 11, 2014 and June 25, 2020.
- Death data is sourced from third party providers and aggregated with administrative claims data and is available for at least half of the CDC-reported deaths in the country.

Study Design

- Retrospective matched cohort observational real-world study evaluating patient outcomes.

Primary Endpoint

- Time to next treatment (TTNT) of 1L ICI, defined as the time from initiation of 1L ICI regimen to the first administration of subsequent line of treatment (LOT) or to patient date of death, whichever occurred first. Pts without any subsequent LOT were censored at their last known activity.
- Real-world overall survival (rwOS) since index date, defined as time from the earliest ctDNA test report date of *KRAS*^{G12C} to date of death. Pts without known date of death were censored at their last documented claim date.

Secondary Endpoints

- Time to treatment discontinuation (TTD) of 1L ICI, defined as time from 1L ICI initiation to the discontinuation of 1L ICI (the date of last administered dose of 1L ICI). Discontinuation events include having a gap of more than 90 days with no subsequent LOT; having a subsequent LOT; or having a date of death while on 1L ICI regimen, whichever occurred first.

Key Inclusion Criteria

- Adult pts treated in the United States
- At least one Guardant360 test with LUAD entered as cancer type on test requisition form
- At least one claim with lung cancer diagnosis ICD-10 code during baseline period, defined as the six month period prior to index
- *KRAS* ^{G12C} mutations detected via Guardant360 test
- Record of 1L PD-1/PD-L1 (including pembrolizumab, atezolizumab, durvalumab or nivolumab) ± chemotherapy (including carboplatin, cisplatin, pemetrexed, paclitaxel, gemcitabine) after first *KRAS*^{G12C} detection
- At least 90 days follow-up
- At least two pharmacy claims during the follow up period
- Confirmed metastatic status during the period of 60 days prior or after index, defined as secondary malignancy ICD-9 or ICD-10 diagnosis code, or claims with metastatic agents.

Exclusion Criteria

- Pts with primary cancer site other than lung and skin (basal, squamous cell carcinoma)
- Pts who received ipilimumab alone or in combination with other ICI and/or chemotherapy agents in 1L
- Pts who received tyrosine kinase inhibitors (TKI) prior to index

Statistical Analyses

- A cohort of pts without *KRAS*^{G12C}, including *KRAS* wildtype (wt) pts and pts with other *KRAS* mutations, were matched on 3:1 ratio. The following characteristics were incorporated into the matching process: age, gender, year of index and baseline Elixhauser Comorbidity Index (ECI).
- Time-to-event analyses were performed using Kaplan-Meier analyses and Cox proportional hazards regression models, to compare the impact of *STK11* mutations in the *KRAS*^{G12C} cohort, and matched cohorts without *KRAS*^{G12C}.
- A sensitivity analysis using maximum permissible gap of 60, 90, or 120 days was conducted to determine the robustness of this definition of discontinuation.

Results

- Two groups were constructed based on the inclusion, exclusion and cohort matching criteria. 330 LUAD pts with *KRAS*^{G12C} and 938 matched LUAD pts without *KRAS*^{G12C} detected were included.
- 754 pts (80%) of the matched cohort were KRAS wildtype (wt), of whom 6% (n=49) had *STK11* mutations (mt).

Figure 1. Detection rate of *STK11* mutations

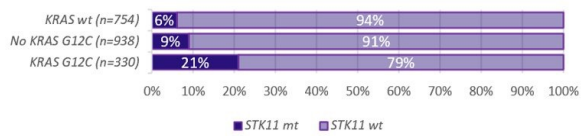


Table 1. Patient demographics and baseline characteristics by *KRAS*^{G12C} and *STK11* status

		STK11 wt (n=260)	*STK11* mt (n=70)	p-value
KRAS$_{G12C}$ LUAD	Age, mean (SD)	68 (10.3)	63.3 (10)	0.0008*
	ECI, mean (SD)	5.7 (3.0)	5.3 (2.7)	0.31
	Age group, n(%)			
	<50	12 (4.6%)	6 (8.6%)	0.055
	50-64	97 (37.2%)	34 (48.6%)	
	65+	152 (58.2%)	30 (42.9%)	
	Female, n(%)	160 (61.3%)	40 (57.1%)	0.53
	Known to be deceased, n(%)	48 (18.4%)	28 (40%)	0.0001*
		STK11 wt (n=854)	*STK11* mt (n=84)	p-value
Matched Cohort without *KRAS*$_{G12C}$	Age, mean (SD)	68 (10.3)	66.1 (8.8)	0.19
	ECI, mean (SD)	7.2 (3.2)	7.0 (3.2)	0.54
	Age group, n(%)			
	<50	35 (4.1%)	2 (2.4%)	0.73
	50-64	311 (35.4%)	32 (38.1%)	
	65+	508 (59.5%)	50 (59.9%)	
	Female, n(%)	527 (61.7%)	45 (53.6%)	0.14
	Known to be deceased, n(%)	215 (25.2%)	28 (33%)	0.10

ECI, Elixhauser Comorbidity Index; mt, mutant; n, number of patients within a group; wt, wild type

Table 2. Multivariate Cox proportional hazard model of time-to-event endpoints

Cohort	Endpoints	HR* (95% CI) *STK11* wt vs. mt	p-value
KRAS$_{G12C}$ (n=330)	TTNT	2.7 (1.8, 4.0)	<.0001
	TTD	1.4 (1.0, 2.0)	0.03
	rwOS	3.2 (2.0, 5.1)	<.0001
No *KRAS*$_{G12C}$ (n=938)	TTNT	1.7 (1.2 2.5)	0.02
	TTD	1.5 (1.0, 2.2)	0.007
	rwOS	1.8 (1.2, 2.8)	0.004
KRAS wt (n=754)	TTNT	1.7 (1.1, 2.6)	0.02
	TTD	1.4 (1.0, 2.0)	0.08
	rwOS	1.4 (0.8, 2.4)	0.3

CI, Confidence internal; HR, hazard ratio; n, number of patients within a group
* Adjusted according to age group, gender and ECI

- Patient demographics and baseline characteristics of both *KRAS*^{G12C} cohort and the matched cohort are presented respectively, in **Table 1.**
- Over 21% of LUAD pts with *KRAS*^{G12C} have co-occurring mutations in *STK11* gene, while only 6% of *KRAS* wt pts and 9% of pts without *KRAS*^{G12C} also have *STK11* mutations.
- In the *KRAS*^{G12C} cohort, pts with *STK11* mutations had statistically significant shorter TTNT (hazard ratio [HR] 2.7, 95% confidence internal [CI] 1.8-4.0, p<0.0001), TTD (HR 1.4, 95% CI 1.0-2.0, p<0.04) and rwOS (HR 3.2, 95% CI 2.0-5.1, p<0.0001) than pts without *STK11* mutations. **(Table 2)**. Median TTNT was over four times shorter and median TTD was almost two times shorter in *STK11* mt vs. *STK11* wt pts (TTNT: 224 vs. 975 days; TTD: 172 vs. 232 days).
- In the matched no *KRAS*^{G12C} cohort, pts with *STK11* mutations had statistically significant shorter TTNT, TTD and OS than pts without *STK11* mutations; however adjusted HRs of TTNT and rwOS were lower compared to those of the *KRAS*^{G12C} cohort **(Table 2)**.
- In the matched *KRAS* wt cohort, the differences in TTD and OS in pts with vs. without *STK11* mutation did not reach statistical significance **(Table 2)**.
- In the *KRAS*^{G12C} cohort, Median rwOS was not reached in the *STK11* wt *KRAS*^{G12C} cohort; however, adjusted hazard ratio (HR) from Cox regression model showed *STK11* mt pts were 3.2 more times likely to die compared to *STK11* wt pts.
- Findings were consistent across sensitivity analyses on the maximum permissible gaps.

Figure 2. Kaplan-meier analysis of real-world outcomes of 1L ICI regimen in LUAD with *KRAS*^{G12C} by *STK11* status

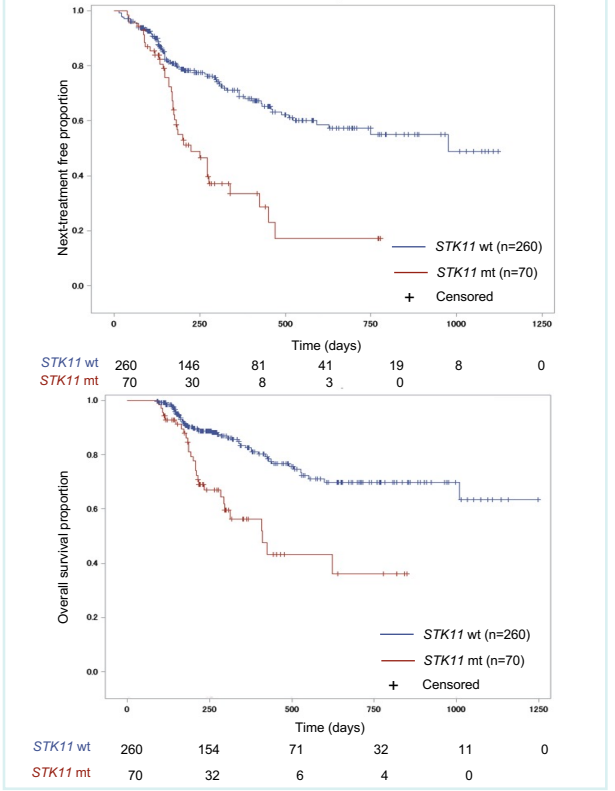
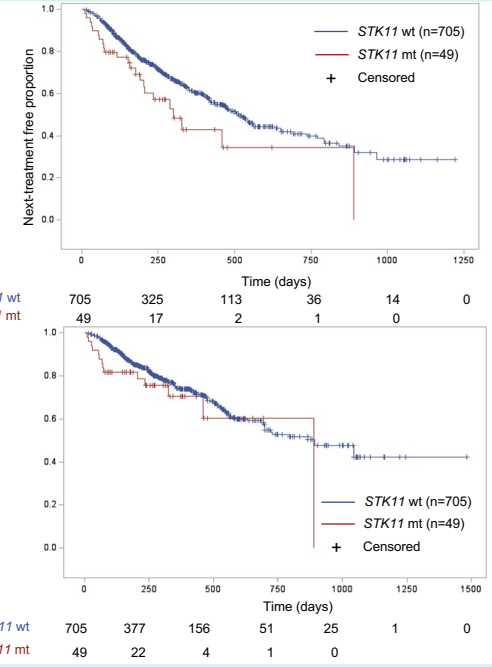


Figure 3. Kaplan-meier analysis of real-world outcomes of 1L ICI regimen in *KRAS* wt LUAD by *STK11* status



Conclusion

- This study provides real-world evidence that *KRAS*^{G12C} and *STK11* co-mutations are associated with poor outcomes in pts treated with ICI in 1L.
- These inferior outcomes indicate a high unmet medical need among LUAD pts harboring co-occurring *KRAS*^{G12C} and *STK11* mutations and demonstrate the need for effective targeted and/or combination therapies in this patient population.

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- Beata Korytowsky, Andrew Chi and Jamie Christensen are employees and shareholders of Mirati Therapeutics, Inc.

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