Relationship between RET fusion partner and treatment outcomes in patients (pts) with non-small cell lung cancer (NSCLC) from the phase I/II ARROW study and real-world data (RWD)

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BACKGROUND

- Previous studies have reported the anti-tumour activity of selective RET inhibitor therapy in patients with *RET*-rearranged non-small cell lung cancer (NSCLC), with tumours harbouring CCDC6 RET fusions displaying greater overall response rates (ORR) and overall survival (OS) than those with KIF5B RET fusions[1–3]
- The highly-selective RET inhibitor pralsetinib is approved by the EMA and FDA for the treatment of advanced *RET* fusion-positive NSCLC[4,5] based on results of the global ARROW study (NCT03037385)[6]
- We examined the relationship between RET fusion partner and treatment outcomes in patients with *RET* fusion-positive NSCLC using data from ARROW and real-world data (RWD)

METHODS

ARROW study

- Phase I dose escalation established the recommended phase II dose of pralsetinib (400 mg once daily, orally) for use in multiple dose-expansion cohorts
- In the *RET* fusion-positive NSCLC cohort, patients ≥18 years with ECOG PS 0–2 and locally documented *RET* fusions received pralsetinib until progression, intolerance or withdrawal
- Phase II primary endpoints were ORR (blinded independent central review per RECIST v1.1) and safety
- Unadjusted Cox regression analyses are presented

RWD

- Data were obtained from patients with advanced *RET* fusion-positive NSCLC meeting eligibility criteria, including no evidence of other cancers, activity or death within 90 days of advanced diagnosis and ≥1 line of therapy, from the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database[7].*

*originated from ~280 US cancer clinics (~800 sites of care), containing retrospective longitudinal clinical data derived from electronic health records that were linked to comprehensive genomic profiling tests data by de-identified, deterministic matching

RESULTS

ARROW study data

- In phase II of ARROW (data cut-off: 6 November 2020), 233 patients with *RET* fusion-positive NSCLC (KIF5B n=164, CCDC6 n=41, Other n=28) were enrolled, of whom 75 were treatment-naïve and 158 had received prior systemic therapy
- Baseline characteristics were balanced across all subgroups (**Table 1**)

Table 1. Patient baseline characteristics (ARROW study)

n (%)	Subgroup	Fusion partner		
		KIF5B (n=164)	CCDC6 (n=41)	Other (n=28)
Age, years	<65 years ≥65 years	103 (62.8) 61 (37.2)	27 (65.9) 14 (34.1)	15 (53.6) 13 (46.4)
Sex	Male Female	77 (47.0) 87 (53.0)	18 (43.9) 23 (56.1)	16 (57.1) 12 (42.9)
Race	White Asian Other	85 (51.8) 65 (39.6) 14 (8.5)	23 (56.1) 15 (36.6) 3 (7.3)	13 (46.4) 12 (42.9) 3 (10.7)
Smoking history	Current/former Never Unknown	57 (34.8) 104 (63.4) 3 (1.8)	16 (39.0) 25 (61.0) 0	11 (39.3) 16 (57.1) 1 (3.6)
ECOG PS	0 1 2	57 (34.8) 101 (61.6) 6 (3.7)	13 (31.7) 28 (68.3) 0	8 (28.6) 20 (71.4) 0
Brain metastases	Yes	62 (37.8)	13 (31.7)	12 (42.9)
SLD	Low High	81 (49.4) 83 (50.6)	23 (56.1) 18 (43.9)	14 (50.0) 14 (50.0)
Prior chemotherapy	Yes	98 (59.8)	24 (58.5)	14 (50.0)
Prior PD-(L)1 inhibitor	Yes	54 (32.9)	10 (24.4)	5 (17.9)
Prior multikinase inhibitor	Yes	29 (17.7)	10 (24.4)	5 (17.9)

PD-(L)1, programmed cell death protein-1 or programmed cell death ligand-1; SLD, sum of longest diameters.

- ORR was comparable in patients whose tumours harboured KIF5B or CCDC6 RET fusions (67.7% vs 68.3%, respectively), but was lower with Other RET fusions (39.3%; **Table 2**)
  - The same ORR trend by RET fusion partner was observed in treatment-naïve patients and in those who had received prior treatment (**Table 2**)
- Disease control rate (DCR) was high in all patients, but lowest in the Other RET fusions subgroup (92.1% KIF5B vs 90.2% CCDC6 vs 82.1% Other; **Table 2**)
- Odds ratios for ORR and DCR comparing CCDC6 vs KIF5B did not change when adjusted for covariates including age, sex, ECOG PS, brain metastases and SLD

Table 2. Efficacy summary by RET fusion partner and prior treatment

Fusion partner	ORR, n/N (%) [95% CI]			DCR n (%) [95% CI]	DOR months [95% CI]	PFS months [95% CI]
	Overall	Treatment naïve	Prior treatment			
KIF5B	111/164 (67.7) [60.0–74.8]	37/50 (74.0) [59.7–85.4]	74/114 (64.9) [55.4–73.6]	151 (92.1) [86.8–95.7]	15.1 [11.0–NR]	12.8 [9.1–17.1]
CCDC6	28/41 (68.3) [51.9–81.9]	11/13 (84.6) [54.6–98.1]	17/28 (60.7) [40.6–78.5]	37 (90.2) [76.9–97.3]	22.3 [22.3–NR]	NR [18.8–NR]
Other	11/28 (39.3) [21.5–59.4]	6/12 (50.0) [21.1–78.9]	5/16 (31.2) [11.0–58.7]	23 (82.1) [63.1–93.9]	NR [10.6–NR]	16.5 [3.7–NR]

CI, confidence interval; DOR, duration of response; NR, not reached; PFS, progression-free survival.

ARROW study data (cont'd)

- Median DOR was higher with CCDC6 vs KIF5B RET fusions (22.3 vs 15.1 months, respectively), regardless of prior therapy (**Table 2** and **Figure 1**)
- Median PFS was also higher with CCDC6 vs KIF5B RET fusions (not reached vs 12.8 months, respectively), irrespective of prior treatment (**Table 2** and **Figure 2**)
- Hazard ratios for DOR and PFS comparing CCDC6 vs KIF5B did not change when adjusted for covariates including age, sex, ECOG PS, brain metastases and SLD
- OS data are currently immature with median OS not reached in any of the RET fusion subgroups (**Figure 3**)

Figure 1. DOR by RET fusion partner and prior treatment

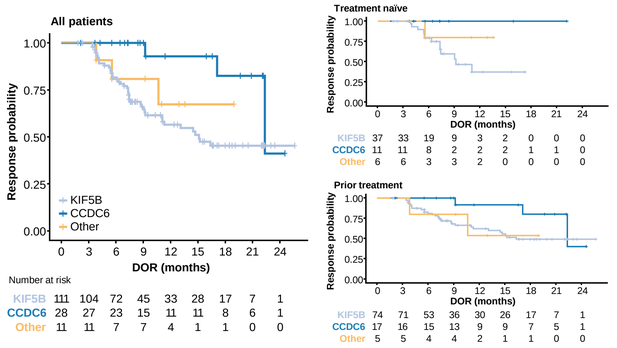


Figure 2. PFS by RET fusion partner and prior treatment

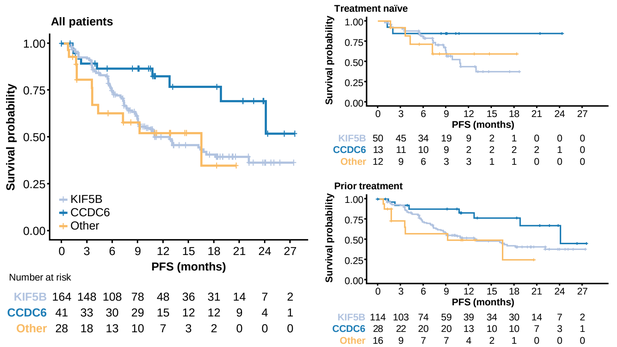
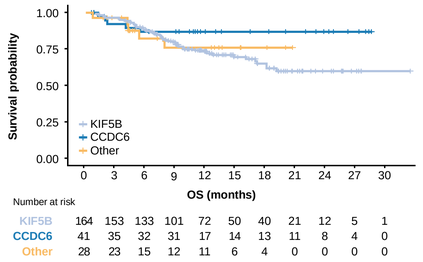


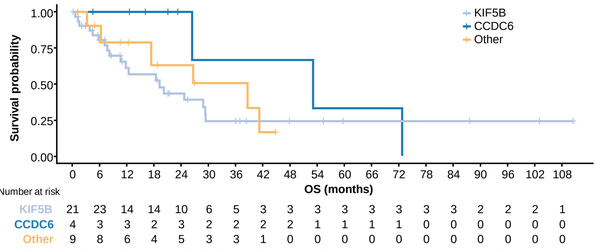
Figure 3. OS by RET fusion partner



RWD

- In Q1 2022, 67 patients with *RET* fusion-positive NSCLC (KIF5B n=46, CCDC6 n=8, Other n=13) met eligibility criteria for the Flatiron Health-Foundation Medicine NSCLC clinico-genomic database
- Median real-world OS was longer with CCDC6 and Other RET fusions vs KIF5B *RET*-driven disease (52.8 and 38.5 vs 19.1 months, respectively; **Figure 4**)
- When adjusted for covariates including RET inhibitor usage (KIF5B n=12, CCDC6 n=5, Other n=5), OS hazard ratios for CCDC6 and Other RET fusions vs KIF5B were 0.49 (95% CI: 0.08–3.11) and 0.41 (95% CI: 0.13–1.30), respectively

Figure 4. Real-world OS* Kaplan-Meier curves by RET fusion partner



*Left-truncated: risk set adjustment to adjust for delayed Foundation Medicine next-generation sequencing testing after index date (first-line start date); patients are only considered at risk once they received the positive *RET* test report

CONCLUSIONS

Data from the phase I/II ARROW study confirm that the highly-selective RET inhibitor pralsetinib is active in patients with *RET* fusion-positive NSCLC, regardless of fusion partner or prior treatment

Our findings in ARROW and RWD support previous studies suggesting that patients with CCDC6 *RET*-driven disease may have a better prognosis than those with KIF5B *RET*-driven disease[1–3]

SUMMARY

Phase II trial data for 233 patients with *RET* fusion-positive NSCLC

RWD for 67 patients with *RET* fusion-positive NSCLC

Comparable ORR with higher DOR and PFS for CCDC6 vs KIF5B RET fusions in the ARROW study

Real-world OS longer with CCDC6 vs KIF5B RET fusions

ARROW OS data currently immature in RET fusion subgroup analysis

Pralsetinib is active in *RET* fusion-positive NSCLC, regardless of fusion partner

CCDC6 *RET*-driven disease may have a better prognosis vs KIF5B

Disclosures

Shirish M. Gadgeel (email address: sgadgee1@hfhs.org) reports an advisory board role for AstraZeneca, Amgen, Roche/Genentech, Bristol Myers Squibb, Pfizer, Novartis, Blueprint Medicines, Daichii; and data safety monitoring board role for AstraZeneca.
For co-author disclosures, please refer to the abstract: https://oncologypro.esmo.org/

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