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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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984P 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: The ARROW study is assessing the anti-tumour activity of pralsetinib, a highly-selective RET inhibitor in advanced solid tumours, including *RET* fusion+ NSCLC. Prolonged overall survival (OS) was reported with RET inhibitor therapy in NSCLC pts with CCDC6 vs KIF5B RET fusions (Tan AC, et al. JTO 2020). We examined the relationship between RET fusion partner and treatment outcomes in pts with *RET* fusion+ NSCLC from ARROW and RWD.

Methods: In phase 2 of ARROW, 233 pts with *RET* fusion+ NSCLC (KIF5B n=164, CCDC6 n=41, Other n=28) received 400mg/day pralsetinib until progression, intolerance or withdrawal. Primary endpoints: overall response rate (ORR) and safety. In Q4 2021, 67 pts with *RET* fusion+ NSCLC (KIF5B n=46, CCDC6 n=8, Other n=13) met eligibility criteria from the nationwide (US-based) de-identified Flatiron Health-FMI NSCLC clinico-genomic database. Cox regression analyses are reported.

Results: Baseline characteristics by RET fusion partner were balanced across subgroups within ARROW. ORR was similar with KIF5B and CCDC6, but lower with Other RET fusions (Table); the same trend was seen in treatment-naïve and prior treatment subgroups. Disease control rate (DCR) was high in all pts, but lowest in the Other RET fusions subgroup. Median duration of response (DOR) and progression-free survival (PFS) were higher with CCDC6 vs KIF5B RET fusions irrespective of prior treatment. OS data are immature. In the RWD cohort, median OS was numerically longer in CCDC6 and Other RET fusions vs KIF5B *RET*-driven disease (52.8 and 38.5 vs 19.1 months); when adjusted for covariates including RET inhibitor usage (KIF5B n=12, CCDC6 n=5, Other n=5), OS HRs 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.

Conclusions: Pralsetinib is active in *RET* fusion+ NSCLC, regardless of fusion partner or prior treatment. CCDC6 *RET*-driven disease may have a better prognosis vs KIF5B.

Clinical trial identification: NCT03037385.

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Table: 984P

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–NA]	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–NA]	NA [18.8–NA]
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]	NA [10.6–NA]	16.5 [3.7–NA]

NA, not achieved.

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985P Tepotinib outcomes according to prior therapies in patients with MET exon 14 (METex14) skipping NSCLC

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Background: Tepotinib is a MET inhibitor approved by the European Commission for patients (pts) with advanced *MET*ex14 skipping NSCLC, with prior immunotherapy (IO) and/or platinum-based chemotherapy (CT). Here, we report the first analysis of tepotinib according to prior therapies from all pts with *MET*ex14 skipping NSCLC in VISION (data cut-off: Feb 20, 2022).

Methods: Pts with advanced/metastatic *MET*ex14 skipping NSCLC, detected by tissue (TBx) and/or liquid biopsy, received 500 mg (450 mg active moiety) tepotinib QD. Primary endpoint: objective response by IRC (RECIST 1.1). Predefined analyses included first-line (1L), second-line (2L), second-or-later line (≥2L), and pts with *MET*ex14 skipping by TBx (T+) — the most widely used detection method.

Results: Of 313 pts enrolled, 149 received tepotinib as ≥2L (median age 70.8 yrs [range, 41—89], 52.3% female, 40.9% had smoking history), and 92 as 2L. Prior treatments include platinum-based CT in 126 pts (84.6%) and IO in 81 pts (54.4%; in 36/92 [39.1%] 2L pts and in 45/57 [78.9%] ≥3L pts); as IO monotherapy in 59 pts (39.6%); as IO-CT in 22 pts (14.8%). Objective response rate (ORR) for 2L pts who received CT alone as 1L was 50.0% (95% CI: 36.1, 63.9) overall and 60.5% (43.4, 76.0) in T+ pts. ORR in 2L pts with prior IO-CT was 62.5% (35.4, 84.8) overall and 63.6% (30.8, 89.1) in T+ pts. Among 164 pts who received tepotinib as 1L (median age 74.0 yrs [range, 47—94], 49.4% female, 53.7% had smoking history), ORR was 56.1% (48.1, 63.8) with mDOR of 46.4 months (13.8, ne). Robust efficacy was also observed in T+ pts. Treatment-related adverse events (TRAEs) occurred in 91.7% of pts (1L: 94.5%, ≥2L: 88.6%, prior IO: 90.1%); 34.2% had Grade ≥3 TRAEs (1L: 40.9%, ≥2L: 26.8%, prior IO: 27.2%) and 14.7% discontinued due to TRAEs (1L: 15.2%, ≥2L: 14.1%, prior IO: 17.3%).

Conclusions: In VISION — the largest study of a MET inhibitor in pts with *MET*ex14 skipping NSCLC — tepotinib demonstrated robust and durable efficacy irrespective of prior therapies and had a tolerable safety profile.

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Table: 985P

Tepotinib efficacy		ORR, % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
1L	Overall (n=164)	56.1 (48.1, 63.8)	46.4 (13.8, ne)	12.6 (9.6, 17.7)	19.1 (13.7, 23.7)
	T+ (n=111)	56.8 (47.0, 66.1)	46.4 (13.4, ne)	15.3 (11.3, ne)	25.9 (17.5, 36.6)
2L	Overall (n=92)	45.7 (35.2, 56.4)	12.6 (8.3, 20.8)	10.9 (8.2, 13.8)	20.0 (15.8, 23.7)
	T+ (n=65)	53.8 (41.0, 66.3)	12.4 (7.0, 20.8)	13.7 (8.2, 19.4)	20.9 (17.7, 32.5)
≥2L	Overall (n=149)	45.0 (36.8, 53.3)	12.4 (9.5, 18.5)	11.0 (8.2, 13.7)	19.6 (15.2, 22.3)
	T+ (n=97)	49.5 (39.2, 59.8)	10.2 (8.3, 18.0)	11.5 (8.2, 16.8)	20.4 (17.0, 26.8)