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Activity and safety of the RET inhibitor vandetanib combined with the mTOR inhibitor everolimus in *RET*-rearranged NSCLC

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Disclosures

- **Relevant:**

Investigator initiated trial. No Pharma funding for this trial.

Will present off label use of Vandetanib and Everolimus

- **Research funding:**

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RET fusions are oncogenic and define an unique clinico-pathological subtype of NSCLC

- RET (REarranged during Transfection) fusions identified in 1-2% of unselected NSCLCs, younger < 60, never smokers.
- ***KIF5B-RET & CCDC6-RET*** are the most common fusions.
- Vandetanib, Cabozantinib, & Lenvatinib have modest single agent activity.
- **Vandetanib:** 3/17 evaluable patients with ORR (18%); PFS 4.5 months, OS 11.6 months.
- **Hypothesis:** The combination of vandetanib (V) and everolimus(E) may overcome resistance to either agent alone in *RET*-rearranged NSCLCs.
- **Pre-clinical:** LC-2/ad (NSCLC) and TPC1 (papillary thyroid cancer) *CCDC6-RET* fusion+ cell lines.
- **Clinical:** V and E were administered PO QD on a 28-day schedule at 300 mg and 10 mg respectively based on the RP2D from the Phase 1 trial.

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Patient characteristics and *RET* fusions

Characteristics	Total 19
Sex	
Male	8 (42%)
Female	11 (58%)
Age	21-76 (Median 59)
ECOG PS	
0-1	17 (89.5%)
2	2 (10.5%)
Prior Lines of Therapy	
0–3	12 (63%)
> 3	7 (37%)
Dose level	
0 (VAN 100 mg, EV 2.5 mg)	0
1 (VAN 200 mg; EV 2.5 mg)	1 (5.2%)
2 (VAN 200 mg; EV 5 mg)	1 (5.2%)
3 (VAN 300 mg; EV 5 mg)	2 (10.5%)
4 (VAN 300 mg; EV 10 mg)	15 (79%)

RET fusions	Total
Tested (NGS and/or FISH)	14 (74%)
RET+ (NGS and/or FISH)	13 (93%)
NGS+	10 (77%)
KIF5B-RET	8 (80%)
CCDC6-RET	2 (20%)
FISH+	5 (38%)
NGS+/FISH+	2 (15%)
NGS+/FISH NA†	8 (61%)
NGS-/FISH+	3 (23%)
RET- (NGS-/FISH NA)	1 (7%)
RET NA	5 (26%)

The concordance rate between NGS and FISH for RET fusion detection was 40%

Activity of vandetanib plus everolimus and outcomes in NSCLC patients

Patient Cohort	ORR	Median OS	Median PFS
All (19)	7 PR (37%), 6 SD (32%), 5 PD (26%; 4 clinical PD) 1 NE (5%, withdrew consent)	8.0 mon, 95% CI (4.1, NR)	4.3 mon, 95% CI (3.2, NR)
***RET*+, NGS and/or FISH (13)**	7 PR (54%), 3 SD, 2 cPD, 1 NE	10 mon, 95% CI (8.0, NR)	4.4 mon, 95% CI (3.4, NR)
***RET*+ , NGS+ (10):**	7 PR (70%), 1 SD, 1 cPD, 1 NE	10 mon, 95% CI (7.5, NR)	8 mon, 95% CI (4.4, NR)
***RET*+, NGS+/FISH+ (2)**	1 PR (50%), 1 SD		
***RET*+, NGS+/FISH NA (8)**	6 PR (75%), 1 cPD, 1 NE		
***RET*+, NGS-/FISH+ (3)**	0 PR (0%), 2 SD, 1 cPD		
***RET*-/NA (6):**	0 PR (0%), 3 SD, 3 PD (2 cPD)	3.8 months	3.0 months
***RET*-, NGS-/FISH NA (1)**	0 PR (0%), 1 SD		
***RET* NA (5)**	0 PR (0%), 2 SD, 3 PD (2 cPD)		

ORR in 10 *RET*+ pts by NGS (2 NGS+/FISH+, 8 NGS+/FISH NA): 7 PR/10 = 70%;

ORR in 4 *RET*- pts by NGS (3 NGS-/FISH+, 1 NGS-/FISH NA): 0 PR/4 = 0%;
P < 0.05 (Fisher exact test)

Conclusions

- RET is druggable. Precision Oncology ! First Combo Rx
- **Preclinically:** V+E is superior to monotherapy in abrogating cell division, RET, MEK and mTOR signaling activation in *RET*+ cancer cells.
- **Clinically:** Well-tolerated. Anti-tumor activity in *RET*+ NSCLC patients, with an ORR of 70% and a median PFS of 8 months in *RET*+ patients by NGS, including in patients with CNS and cabozantinib-refractory disease.
- In FISH+, but NGS- patients, 0/3 responses seen, suggesting **NGS may be preferable to FISH for predicting response to RET inhibitors.**

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