Clinical impact of selpercatinib and pralsetinib dose reductions in advanced RET-rearranged NSCLC

William J Phillips[1], Sarah Waliany[2], Joyce Liang[2], **Urs Weber[1]**, Upal B Roy[3], Junxiao Hu[4], Omaima Salous[5], Hiliary Hammell[6], D Ross Camidge[1], Jessica J Lin[2], Tejas Patil[1]

1. Department of Medicine, University of Colorado Cancer Center, Aurora, Colorado; 2. Mass General Brigham Cancer Institute, Boston, Massachusetts; 3. LUNGevity Foundation, Chicago, Illinois; 4. University of Colorado Cancer Center Biostatistics, Aurora, Colorado; 5. Hamoui Foundation, Needham, Massachusetts; 6. RETpositive, Chagrin Falls, Ohio

INTRODUCTION

- Selective RET inhibitors have improved outcomes for patients with RET-rearranged NSCLC
- However, targeted therapy is associated with chronic and cumulative toxicities
- Dose reductions are often used to improve the long-term tolerability
- The impact of dose reduction on efficacy is unknown

AIMS

1. To characterize the association of RET-TKI dose reductions and clinical outcomes
2. To assess whether dose reductions increased the risk of CNS progression

METHODS

- Multicenter retrospective cohort study involving the University of Colorado and Mass General Brigham Cancer Institute
- Adult patients with advanced RET-rearranged NSCLC treated with selpercatinib or pralsetinib, without history of prior RET inhibitors
- Primary endpoints were real-world progression-free survival (PFS) and time to next systemic therapy (TTNT)
- Secondary endpoint was the site of disease progression
- Time dependent Cox Proportional hazards model was used for time-to-event analysis
- Chi-squared test to evaluate differences in sites of progression

CONCLUSIONS

1. Dose reduction of selective RET inhibitors were common in the real-world (19/46, 41%).
2. Dose reduction was not associated with inferior clinical outcomes, including PFS or TTNT.
3. The incidence of CNS progression was comparable in patients who underwent a dose reduction and those who did not.
4. These findings suggest that dose modification of selective RET inhibitors may improve the long-term tolerability of therapy without compromising clinical outcomes.

BASELINE CHARACTERISTICS

Characteristic	Classification	Overall (%)	Standard dose (%)	Dose reduction (%)
Total	-	46	27 (59)	19 (41)
Age	Median (Q1-Q3)	63 (54-69)	62 (48-69)	64 (58-72)
Site	Colorado	32 (70)	18 (67)	14 (74)
	MGH	14 (30)	9 (33)	5 (26)
Sex	Female	20 (43)	13 (43)	7 (44)
	Male	26 (57)	17 (57)	9 (56)
Treatment	Selpercatinib	35 (76)	22 (81)	13 (68)
	Pralsetinib	11 (24)	5 (19)	6 (32)
Line of therapy	First-line	27 (59)	23 (85)	4 (21)
	Later line	19 (41)	4 (15)	15 (79)
Baseline brain imaging	Performed	43 (94)	25 (93)	18 (95)

Table 1: Baseline patient characteristics

CLINICAL OUTCOMES

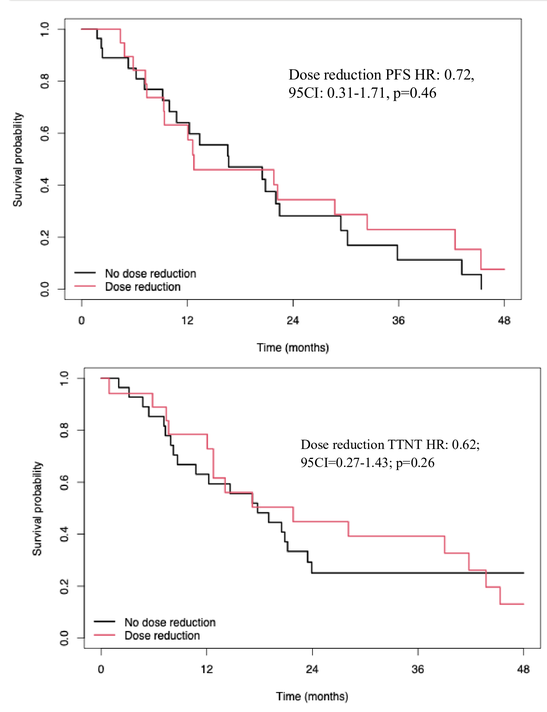


Figure 1: Simon-Makuch plots of progression-free survival (top) and time to next systemic therapy (bottom) stratified by RET TKI dose reduction.
** Models adjusted for line of therapy identified as a possible confounder*
** Median follow-up 40 months*

DOSE REDUCTION

- Dose reductions occurred in 19 (41%) patients
- Median time to dose reduction was 8 weeks (Q1-Q3: 5-20)
- Eleven (58%) patients dose reduced for at least one laboratory abnormality

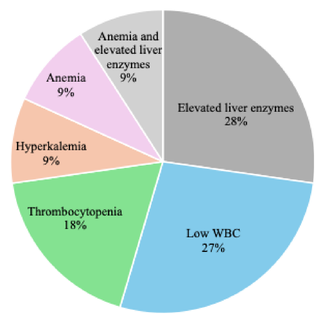


Figure 2: Laboratory reasons for dose reduction of selective RET inhibitors, n=11.

PROGRESSION PATTERNS

- Thirty-eight patients developed disease progression:
 - 25 (66%) with non-CNS only
 - 8 (21%) with CNS only
 - 5 (13%) with non-CNS and CNS
- CNS progression rates were not different between standard dose and dose reduced cohorts (p=0.55)

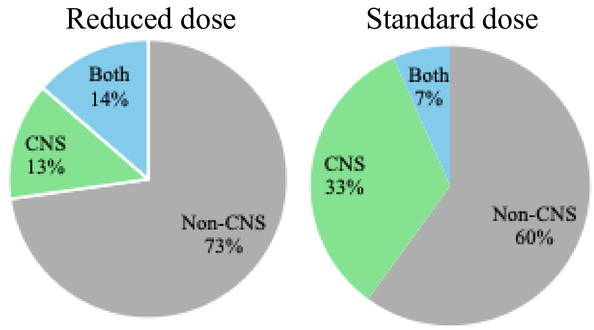


Figure 3: Sites of progression in patients who (left) underwent a dose reduction and (right) did not.