

Mechanisms of Resistance to Selpercatinib in *RET*-Activated NSCLC and MTC from the LIBRETTO-001 Trial

Benjamin J Solomon¹, Alexander Drilon², Lori J Wirth³, Daniel SW Tan⁴, Anna M Szpurka⁵, Ashish C Massey⁵, Xi Rao⁵, Scott S Barker⁵, Jennifer Wright⁵, Helen Won⁵, Maria E Cabanillas⁶

¹Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia; ²Memorial Sloan Kettering Cancer Center, NY, USA; ³ Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA; ⁴National Cancer Centre Singapore, Singapore; ⁵Eli Lilly and Company, Indianapolis, IN, USA; ⁶MD Anderson Cancer Center, Houston, TX, USA

Study was sponsored by Eli Lilly and Company

OBJECTIVE

- This study aims to expand our understanding of mechanisms of resistance and guide treatment strategies against potent RET inhibition using a subset of 115 trial patients
- What are the different types of acquired resistance and their frequencies
 - Are there any differences seen between NSCLC versus MTC

CONCLUSIONS

- Overall, acquired mechanisms of resistance were identified in 45% of ctDNA at the time of disease progression in the largest prospective dataset studying mechanisms of resistance to RET inhibition
- Mechanisms of resistance differ depending on tumor type
 - On target mechanisms of resistance were more common in MTC than NSCLC (43% vs 13%, respectively)
 - Bypass mechanisms of resistance (30%) included RAS/RAF activating alterations and potentially targetable *MET* amplifications
- Overall results suggest that RET was still a driver of progression for a large subset of MTC patients who might benefit from a second generation of RET inhibitor
- PD of most NSCLC patients was driven by non-RET-driven mechanisms which requires more comprehensive genetic testing to characterize
- More comprehensive strategies for testing may be needed to study the 55% of patients with unknown mechanisms of resistance and to optimally guide sequences of therapy and post-selpercatinib treatment strategies

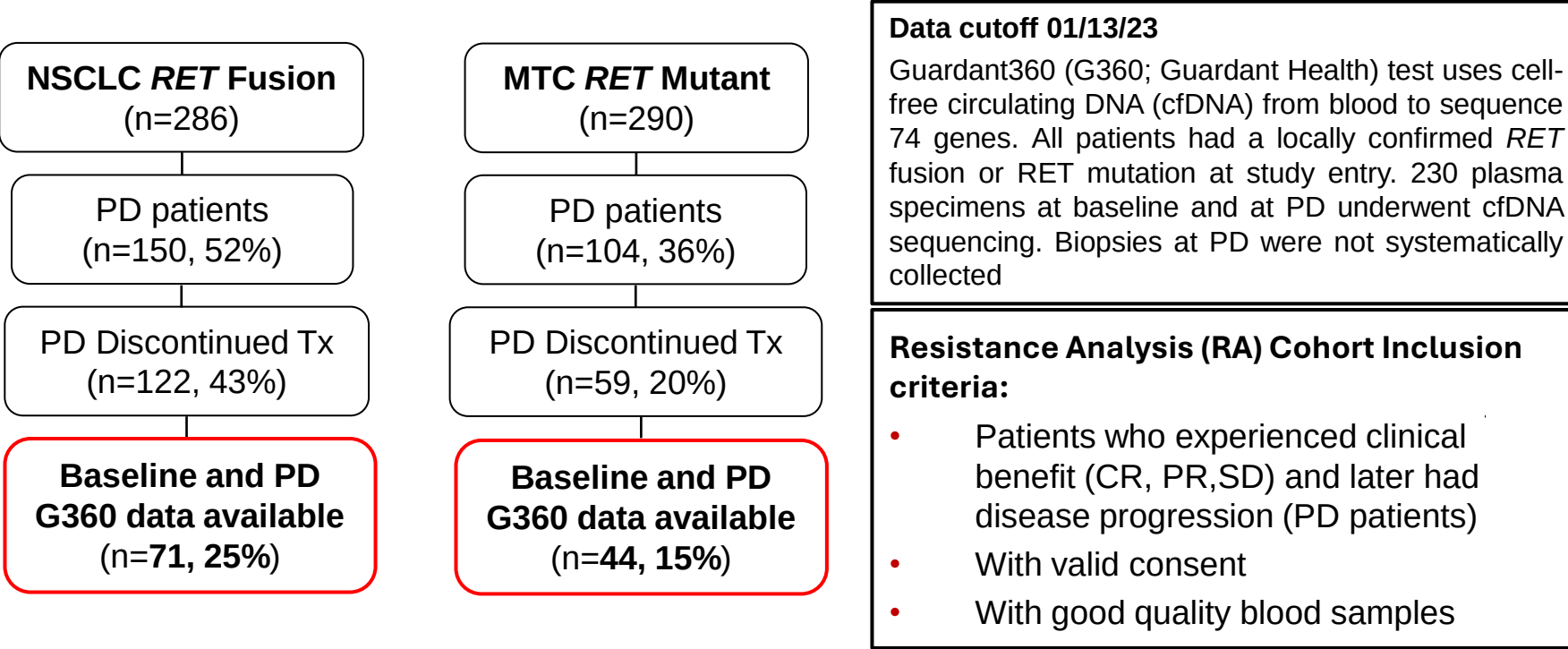


Scan the QR code for a list of all Lilly content presented at the congress.
Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.
Other company and product names are trademarks of their respective owners.

BACKGROUND

- The phase 1/2 LIBRETTO-001 trial (NCT03157128) led to approval of selpercatinib treatment for RET altered solid tumors including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC)
- While the clinical responses to selpercatinib are impressive, emergence of resistance to selpercatinib in treated patients may occur
- Acquired resistance to selpercatinib occurs via on-target alterations and off-target downstream pathway activation and can be driven by
 - Mutations within the RET gene which induce resistance (e.g. solvent front mutations)
 - Upregulation of bypass pathways (e.g. MET amplifications)

STUDY DESIGN



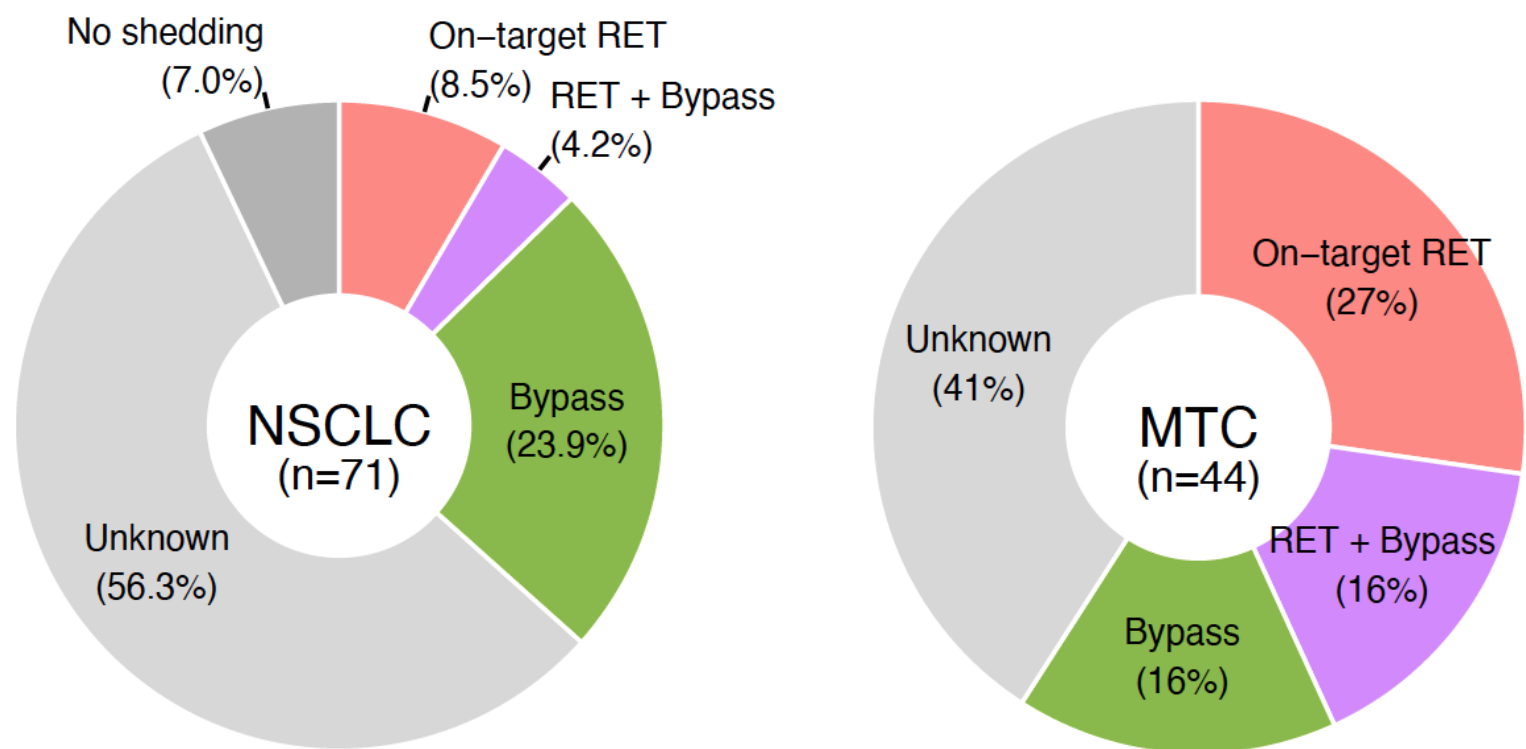
Characteristic	NSCLC cohort (n=71)	MTC cohort (n=44)
Age, years		
Median (range)	58 (30,77)	56 (22,76)
Sex, No. (%)		
Female	43 (61)	16 (36)
Male	28 (39)	28 (64)
Race, No. (%)		
White	39 (55)	40 (91)
Asian	24 (34)	2 (5)
Black	5 (7)	0 (0)
Others	3 (4)	2 (5)
Smoking history, No. (%)		
Current smoker	1 (1)	1 (2)
Former smoker	18 (25)	9 (20)
Never a smoker	52 (73)	33 (75)
Missing	0 (0)	1 (2)
Line of therapy, No. (%)		
1st line	17 (24)	5 (11)
2nd line	44 (62)	35 (80)
Others	10 (14)	4 (9)
Previous multitargeted kinase inhibitor, No. (%)		
Yes	11 (15)	36 (82)
No	60 (85)	8 (18)
<i>RET</i> enrolling alteration, No. (%)		
KIF5B-RET: 51 (72)		M918T: 26 (59)
CCDC6-RET: 9 (13)		V804M/L: 1 (2)
NCOA4-RET: 1 (1)		Extracellular cysteine: 8 (18)
Others/Unknown: 10 (14)		Others: 9 (20)
Local lab assay for <i>RET</i> enrolling alteration, No. (%)		
Tissue based	64 (90)	41 (93)
NGS	59 (83)	30 (68)
PCR (or FISH/others)	5 (7)	11 (25)
Liquid biopsy	7 (10)	3 (7)

* RA patients had similar demographic and baseline characteristics as the overall and PD discontinued patients.

RESULTS

Acquired mechanisms of resistance were identified in 45% (52/115) of Resistance Analysis patients

- On-target resistance mechanisms were identified more frequently in MTC vs NSCLC patients, 43% vs 13%, respectively

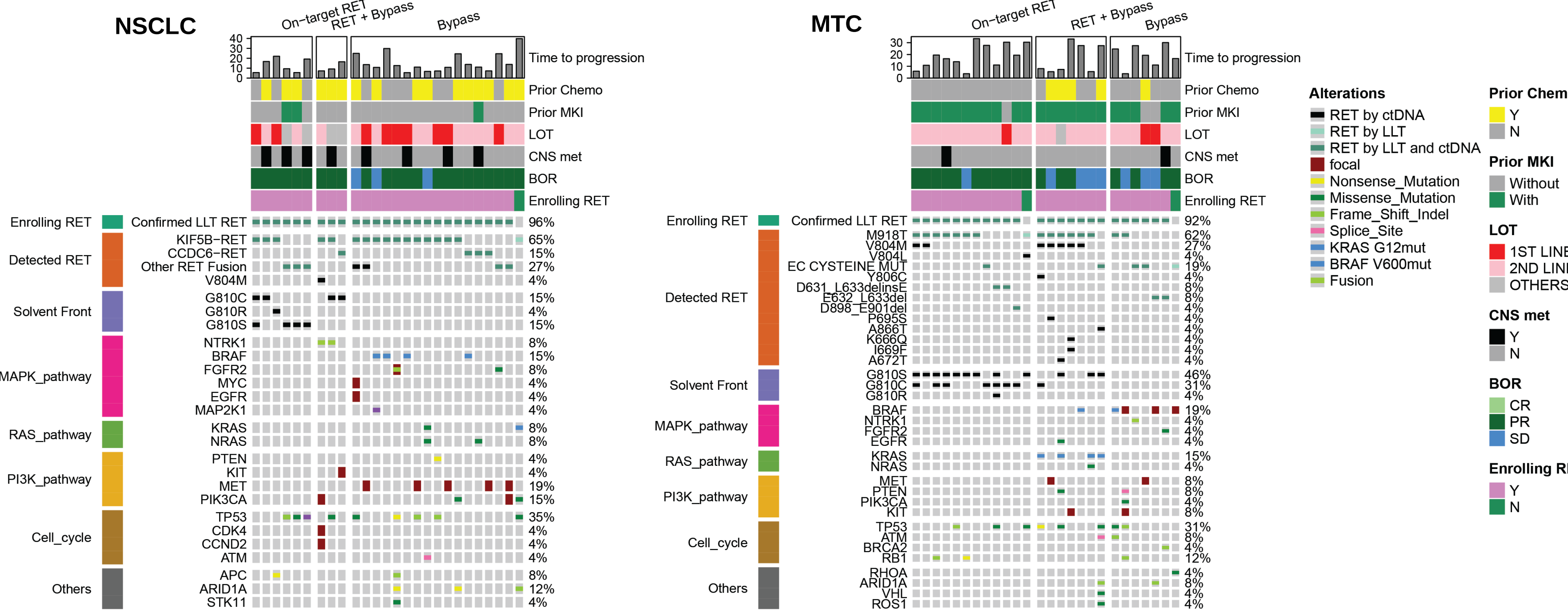


	NSCLC N (%)	MTC N (%)	All patients N (%)
Resistance mechanism	26 (37)	26 (59)	52 (45)
Unknown/No shedding*	45 (63)	18 (41)	63 (55)
On-target	9 (13)	19 (43)	28 (24)
<i>RET</i> Solvent Front G810C/S/R	8	16	24
<i>RET</i> V804M/L**	1	8	9
<i>RET</i> V804M/L** and G810C/S	0	5	5
Bypass	20 (28)	14 (32)	34 (30)
<i>BRAF</i> V600E/Amplification	4	5	9
<i>KRAS</i> G12D/R	1	4	5
<i>MET</i> Amplification	5	2	7
<i>NTRK1</i> fusion	2	1	3
Other***	8	2	10

*patients with no oncogenic alterations detected at baseline.
**1 NSCLC and 1 MTC patient acquired *RET* V804M alone; 4 MTC patients had clonal expansion of *RET* V804M/L with other acquired on-target *RET* alterations; 3 MTC patients acquired *RET* V804M with other acquired on-target *RET* alterations
****EGFR*/*MYC* amplification, *FGFR2* N82S/ P253L/amplification, *KIT* amplification, *KRAS* Q61H, *PIK3CA* E545K, *NRAS* Q61K/L.

Mechanisms of resistance were identified in 37% (26/71) of NSCLC patients and 59% (26/44) of MTC patients

- Mechanisms of resistance includes both acquired variants at progression and primary variants with clonal expansion at progression



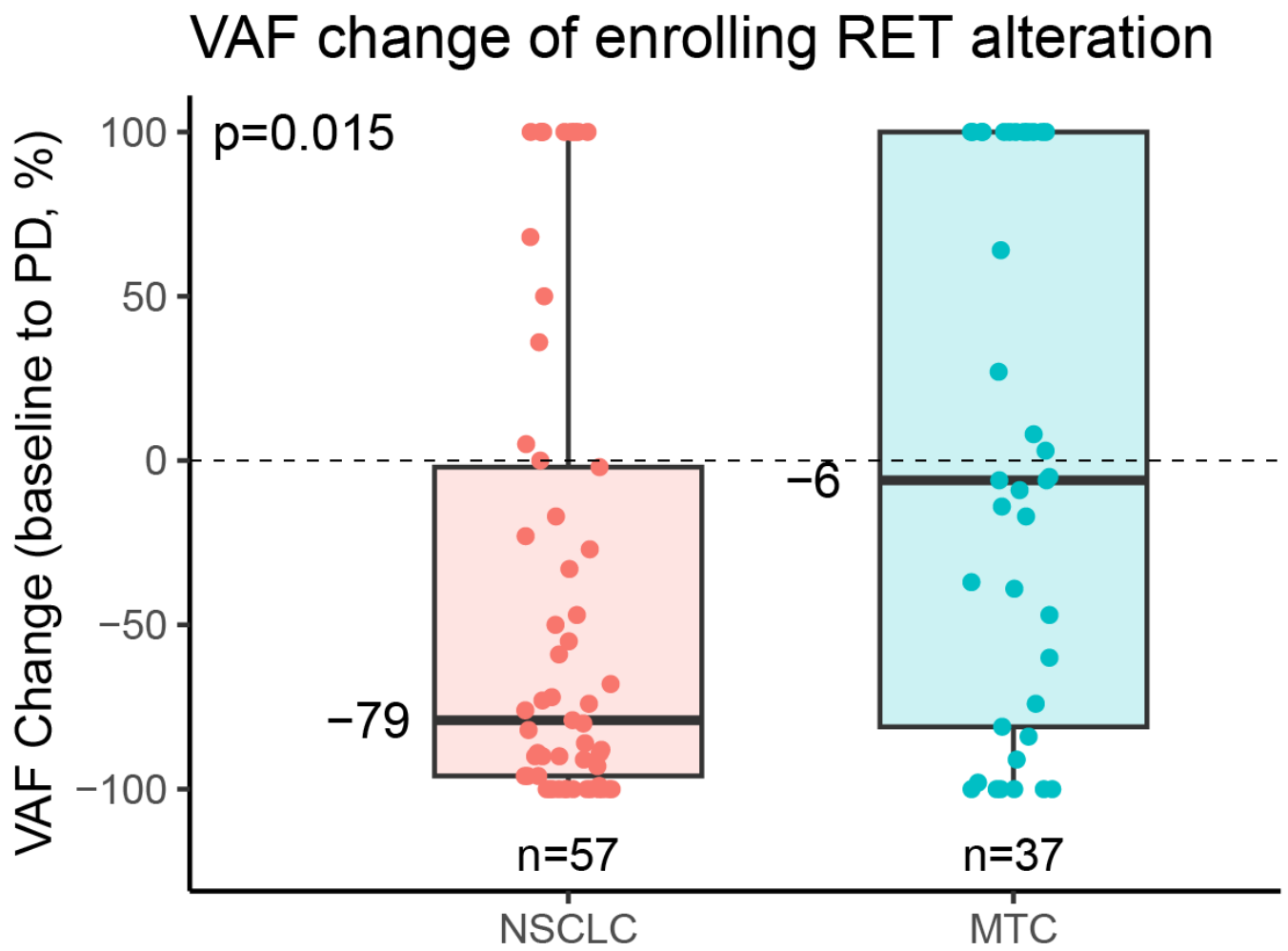
For NSCLC patients

- RET* solvent front mutation was the most prevalent on-target *RET* alteration:
 - G810C/S/R was found in 11% (8/71)
 - V804M/L was found in 1% (1/71)
- 17% (12/71) had bypass alterations in MAPK/RAS pathway:
 - MET* amplification was found in 7% (5/71)
 - BRAF* V600E was found in 6% (4/71)
 - NTRK1* fusion was found in 3% (2/71)
 - KRAS* G12R was found in 1% (1/71)

For MTC patients

- RET* solvent front mutation was the most prevalent on-target *RET* alteration:
 - G810C/S/R was found in 36% (16/44)
 - V804M/L was found in 18% (8/44)
 - V804M/L and G810C/S together was found in 11% (5/44)
- 10% (11/44) had bypass alteration in MAPK/RAS pathway:
 - BRAF* V600E was found in 5% (2/44)
 - BRAF* amplification was found in 7% (3/44)
 - KRAS* G12D/R was found in 9% (4/44)

Selpercatinib suppressed enrolling *RET* driver alterations at progression in NSCLC



- 57/71 (80%) NSCLC patients and 42/44 (95%) MTC patients had *RET* alterations detected at enrollment also confirmed in ctDNA at baseline. 37 MTC patients were included in the plot and 5 were excluded due to suspected germline *RET* variants

- At disease progression, selpercatinib continued suppressing variant allele frequency (VAF) of enrolling *RET* alterations in most NSCLC patients but not in MTC patients (median VAF change: -79% vs -6%; Wilcoxon Signed Rank test: p=0.015)

ACKNOWLEDGMENTS

- We would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible
- We would like to thank the trial investigators and study staff
- Medical writing support was provided James Hegarty of Eli Lilly and Company

Disclosures

Benjamin J Solomon has the following disclosures: Received compensation (institutional or personal) for speaker or advisory roles from AstraZeneca, Pfizer, Amgen, Roche-Genentech, Novartis, Merck, Bristol Myers Squibb, Eli Lilly and Company, Takeda, Janssen. Member of board of directors for Cancer Council of Victoria and Thoracic Oncology Group of Australasia. Received royalties from UpToDate. Served as a steering committee member for Roche-Genentech, Pfizer, Novartis.

Mechanisms of resistance to selpercatinib in *RET*-activated NSCLC and MTC from the LIBRETTO-001 trial

Benjamin J Solomon¹, Alexander Drilon², Lori J Wirth³, Daniel SW Tan⁴, Anna M Szpurka⁵, Ashish C Massey⁵, Xi Rao⁵, Scott S Barker⁵, Jennifer Wright⁵, Helen Won⁵, Maria E Cabanillas⁶

¹Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia; ²Memorial Sloan Kettering Cancer Center, NY, USA; ³ Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, USA; ⁴*National Cancer Centre Singapore, Singapore*; ⁵Loxo@Lilly, Eli Lilly and Company, Indianapolis, IN, USA; ⁶MD Anderson Cancer Center, Houston, TX, USA

The Lilly logo, featuring the word "Lilly" in a white, elegant script font, positioned in the bottom right corner of the slide.

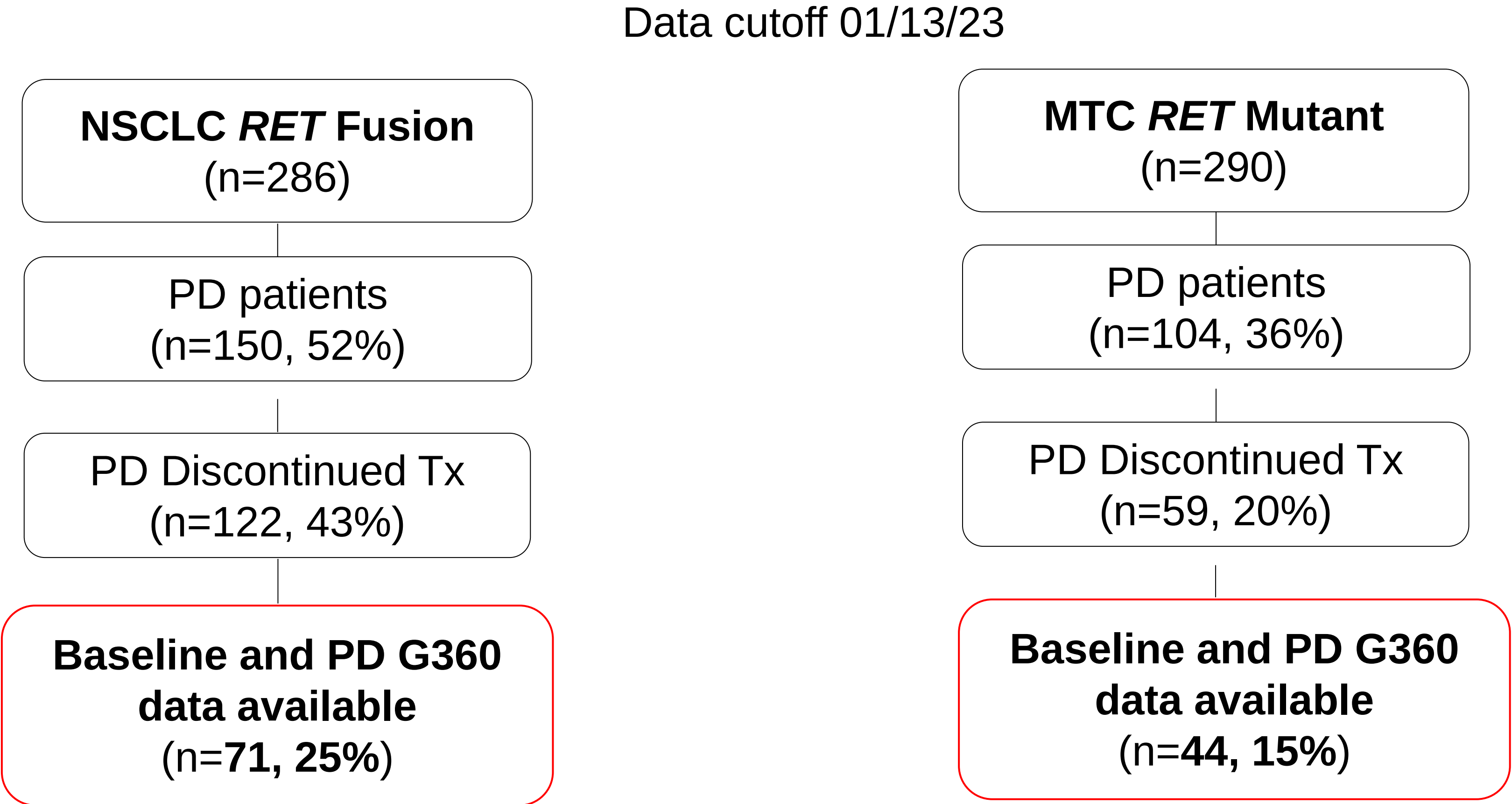
Background

- The phase 1/2 LIBRETTO-001 trial (NCT03157128) led to approval of selpercatinib treatment for *RET* altered solid tumors including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC)
- While the clinical responses to selpercatinib are impressive, emergence of resistance to selpercatinib in treated patients may occur
- Acquired resistance to selpercatinib occurs via on-target alterations and off-target downstream pathway activation and can be driven by
 - Mutations within the *RET* gene which induce resistance (e.g. solvent front mutations)
 - Upregulation of bypass pathways (e.g. MET amplifications)

Objectives

- This study aims to expand our understanding of mechanisms of resistance and guide treatment strategies against potent *RET* inhibition using a subset of 115 trial patients
 - What are the different types of acquired resistance and their frequencies
 - Are there any differences seen between NSCLC versus MTC

Study Design



Resistance Analysis (RA) Cohort Inclusion criteria:

- Patients who experienced clinical benefit (CR, PR,SD) and later had disease progression (PD patients)
- With valid consent
- With good quality blood samples

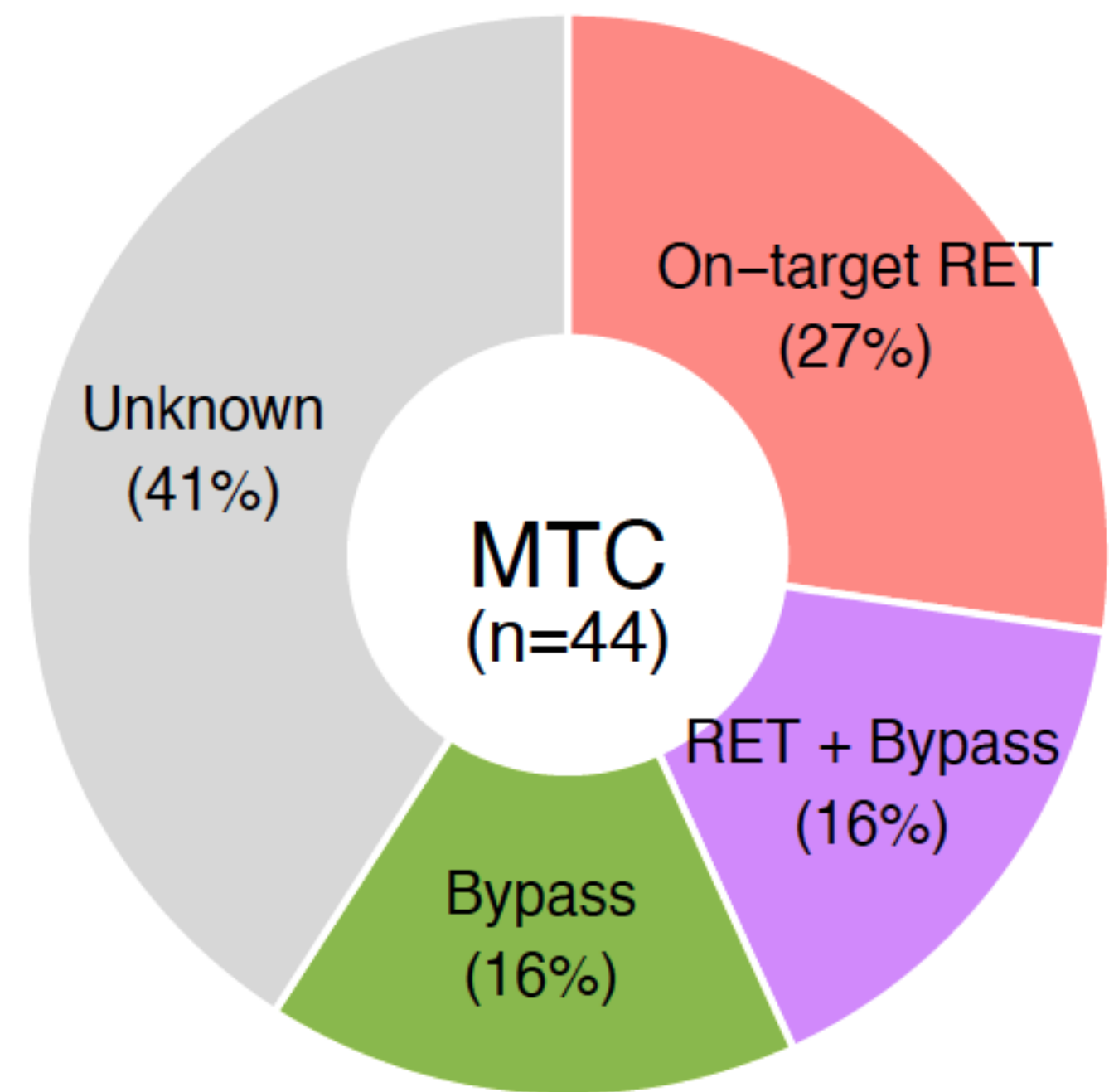
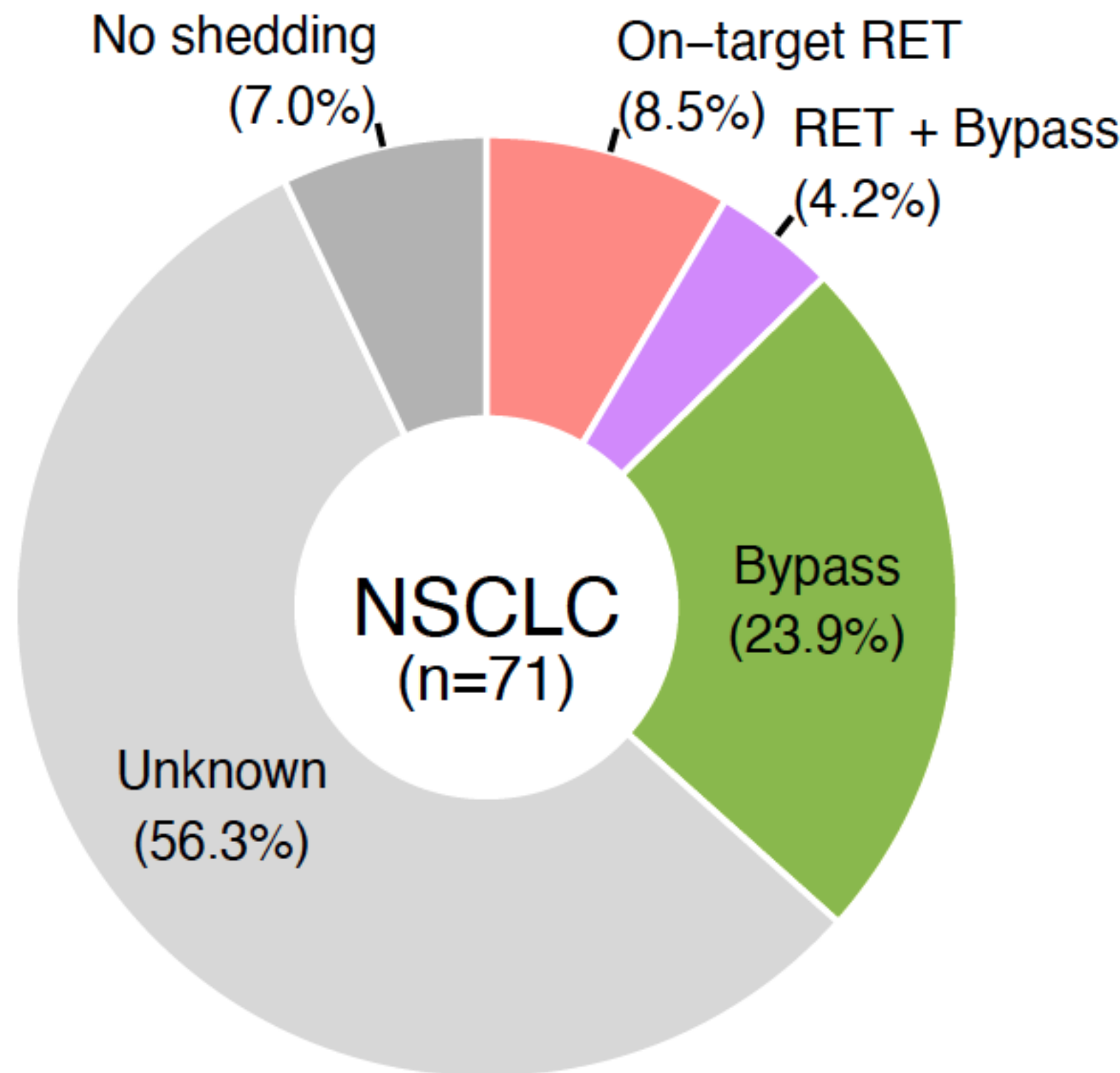
Guardant360 (G360; Guardant Health) test uses cell-free circulating DNA (cfDNA) from blood to sequence 74 genes. All patients had a locally confirmed *RET* fusion or *RET* mutation at study entry. 230 plasma specimens at baseline and at PD underwent cfDNA sequencing. Biopsies at PD were not systematically collected.

Study Design

Characteristic	NSCLC cohort (n=71)	MTC cohort (n=44)
Age, years		
Median (range)	58 (30,77)	56 (22,76)
Sex, No. (%)		
Female	43 (61)	16 (36)
Male	28 (39)	28 (64)
Race, No. (%)		
White	39 (55)	40 (91)
Asian	24 (34)	2 (5)
Black	5 (7)	0 (0)
Others	3 (4)	2 (5)
Smoking history, No. (%)		
Current smoker	1 (1)	1 (2)
Former smoker	18 (25)	9 (20)
Never a smoker	52 (73)	33 (75)
Missing	0 (0)	1 (2)
Line of therapy, No. (%)		
1st line	17 (24)	5 (11)
2nd line	44 (62)	35 (80)
Others	10 (14)	4 (9)
Previous multitargeted kinase inhibitor, No. (%)		
Yes	11 (15)	36 (82)
No	60 (85)	8 (18)
RET enrolling alteration, No. (%)		
KIF5B-RET: 51 (72)		M918T: 26 (59)
CCDC6-RET: 9 (13)		V804M/L: 1 (2)
NCOA4-RET: 1 (1)		Extracellular cysteine: 8 (18)
Others/Unknown: 10 (14)		Others: 9 (20)
Local lab assay for RET enrolling alteration, No. (%)		
Tissue based	64 (90)	41 (93)
NGS	59 (83)	30 (68)
PCR (or FISH/others)	5 (7)	11 (25)
Liquid biopsy	7 (10)	3 (7)

* RA patients had similar demographic and baseline characteristics as the overall and PD discontinued patients.

Acquired mechanism of resistance were identified in 45% (52/115) of Resistance Analysis patients



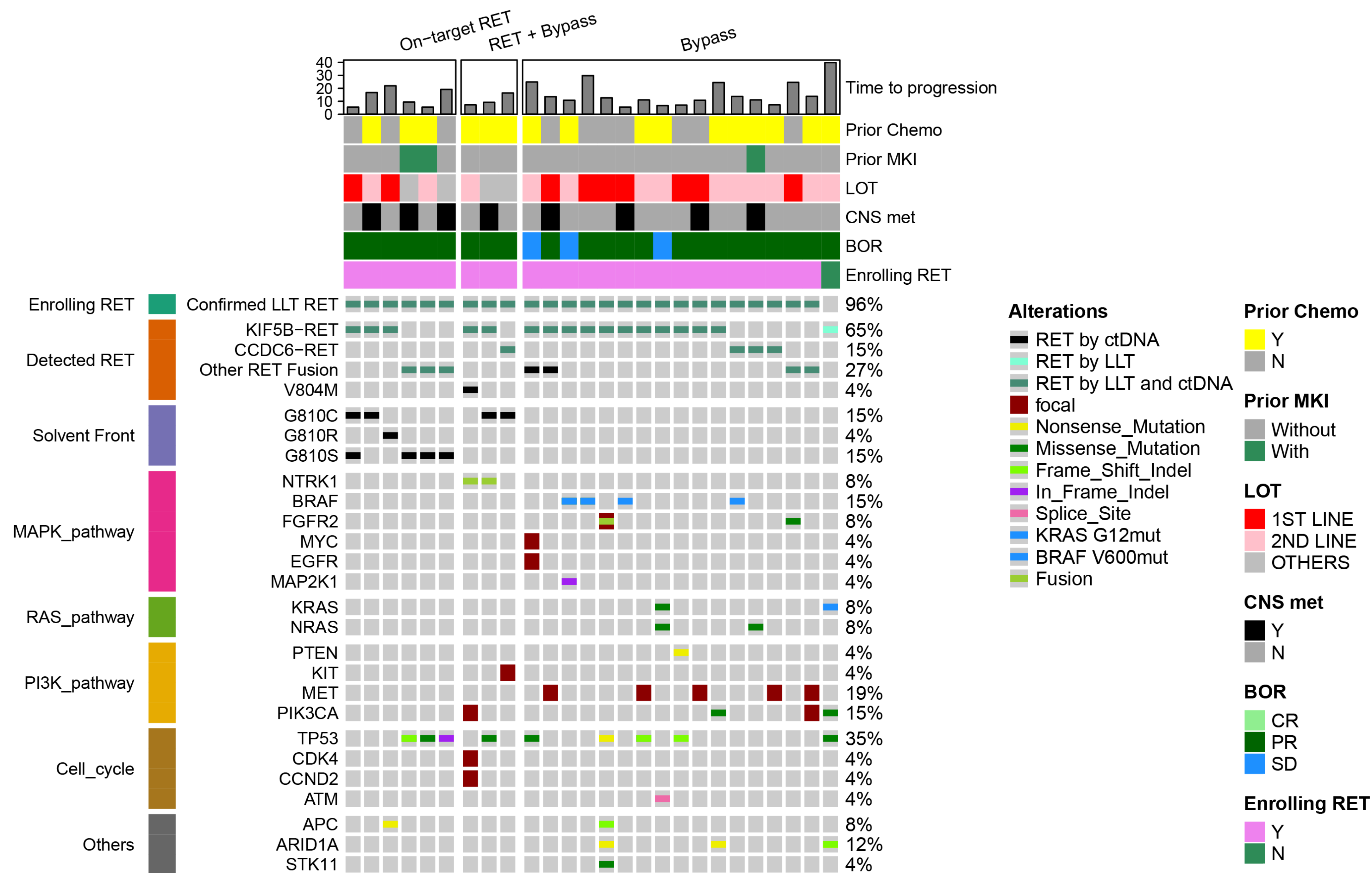
	NSCLC N (%)	MTC N (%)	All patients N (%)
Resistance mechanism	26 (37)	26 (59)	52 (45)
Unknown/No shedding*	45 (63)	18 (41)	63 (55)
On-target	9 (13)	19 (43)	28 (24)
RET Solvent Front G810C/S/R	8	16	24
RET V804M/L**	1	8	9
RET V804M/L** and G810C/S	0	5	5
Bypass	20 (28)	14 (32)	34 (30)
BRAFV600E/Amplification	4	5	9
KRAS G12D/R	1	4	5
MET Amplification	5	2	7
NTRK1 fusion	2	1	3
Other***	8	2	10

*patients with no oncogenic alterations detected at baseline.
**1 NSCLC and 1 MTC patient acquired RET V804M alone; 4 MTC patients had clonal expansion of RET V804M/L with other acquired on-target RET alterations; 3 MTC patients acquired RET V804M with other acquired on-target RET alterations;
***EGFR/MYC amplification, FGFR2 N82S/ P253L/amplification, KIT amplification, KRAS Q61H, PIK3CA E545K, NRAS Q61K/L.

- On-target resistance mechanisms were identified more frequently in MTC vs NSCLC patients, 43% vs 13%, respectively

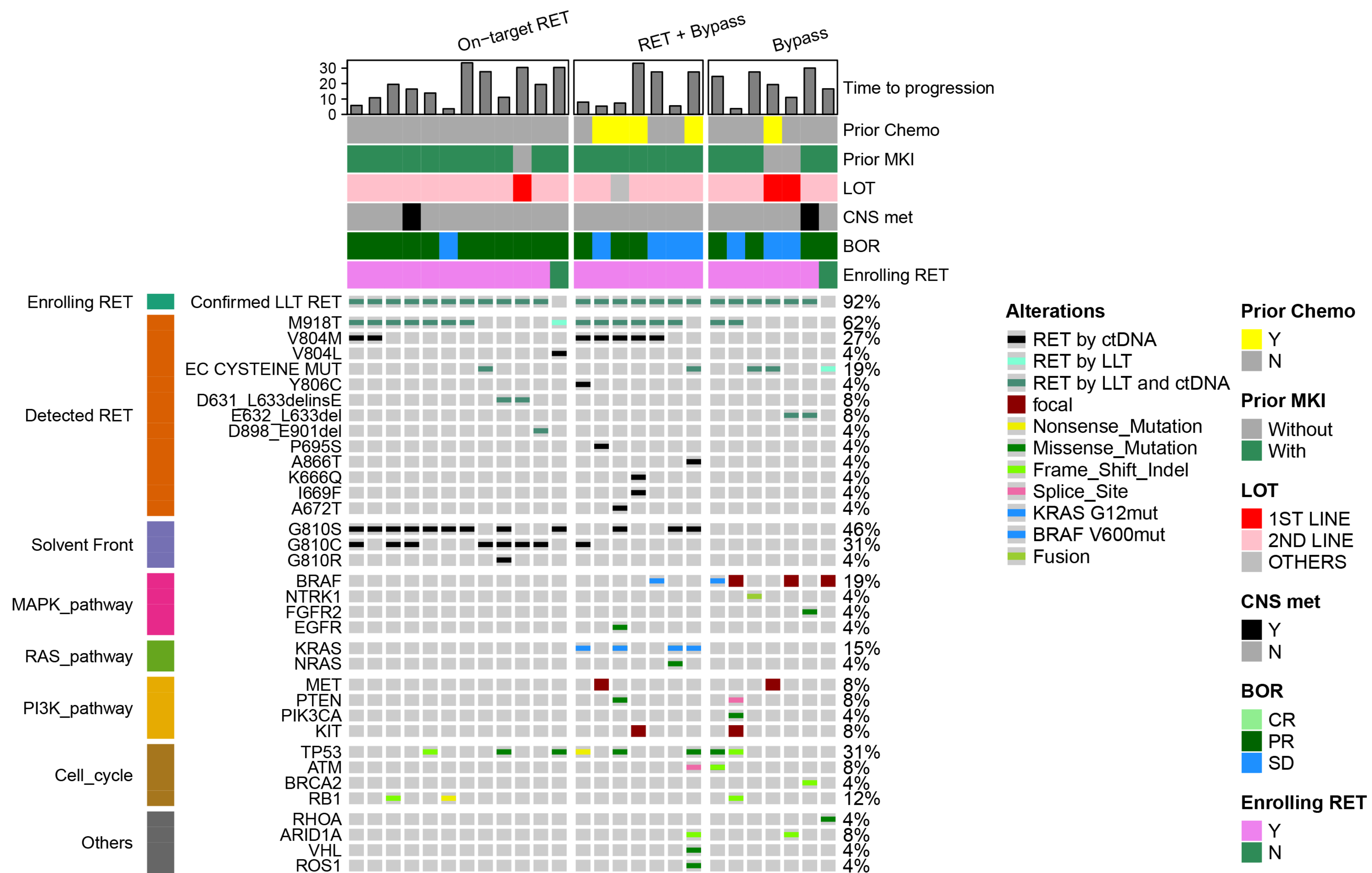
Mechanisms of resistance were identified in 37% (26/71) of NSCLC patients

- Mechanisms of resistance includes both acquired variants at progression and primary variants with clonal expansion at progression



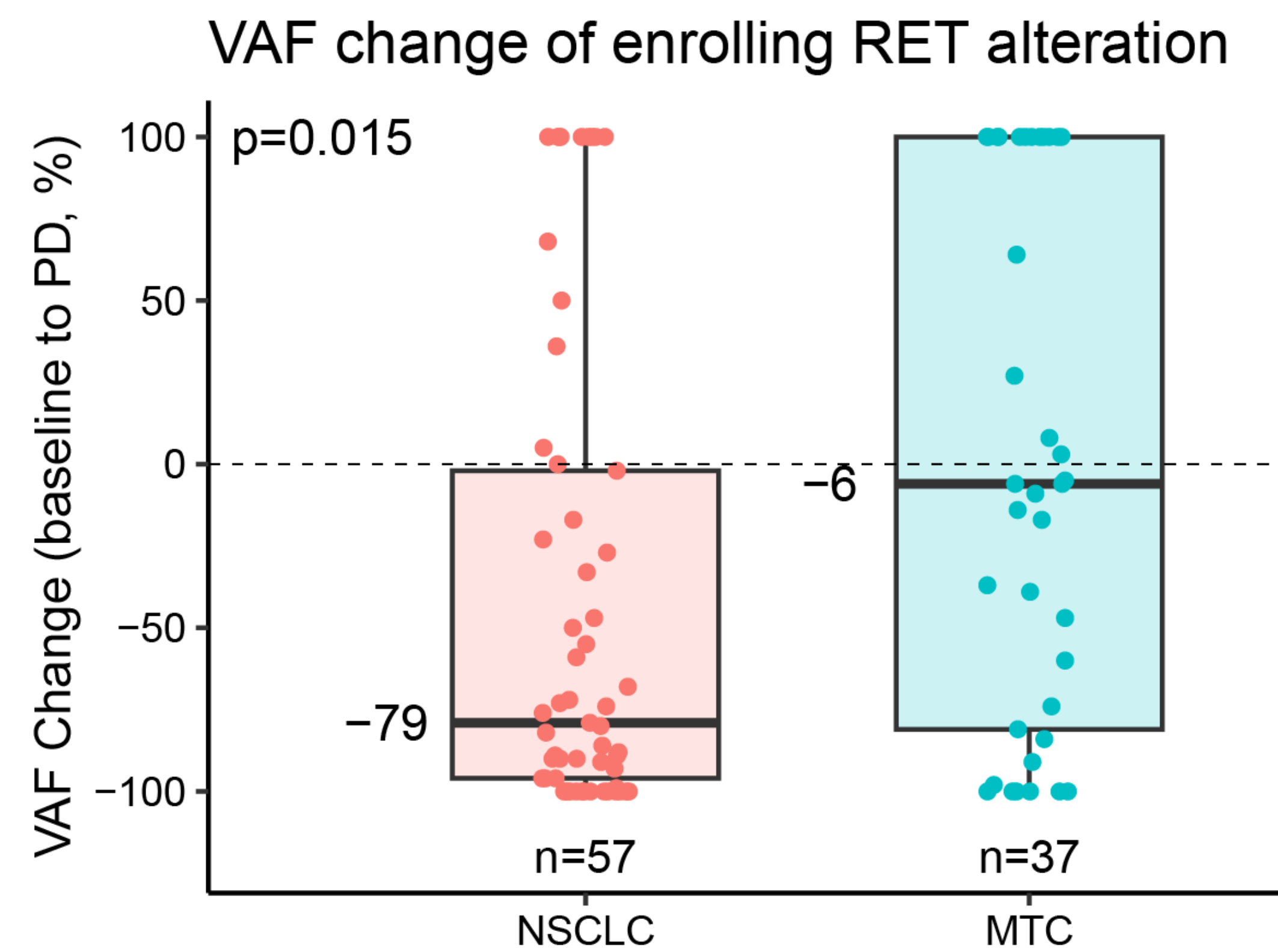
- RET* solvent front mutation was the most prevalent on-target *RET* alteration:
 - G810C/S/R was found in 11% (8/71)
 - V804M/L was found in 1% (1/71)
- 17% (12/71) had bypass alterations in MAPK/RAS pathway:
 - MET* amplification was found in 7% (5/71)
 - BRAF* V600E was found in 6% (4/71)
 - NTRK1* fusion was found in 3% (2/71)
 - KRAS* G12R was found in 1% (1/71)

Mechanisms of resistance were identified in 59% (26/44) of MTC patients



- *RET* solvent front mutation was the most prevalent on-target *RET* alteration:
 - G810C/S/R was found in 36% (16/44)
 - V804M/L was found in 18% (8/44)
 - V804M/L and G810C/S together was found in 11% (5/44)
- 10% (11/44) had bypass alteration in MAPK/RAS pathway:
 - *BRAF* V600E was found in 5% (2/44)
 - *BRAF* amplification was found in 7% (3/44)
 - *KRAS* G12D/R was found in 9% (4/44)

Selpercatinib suppressed enrolling *RET* driver alterations at progression in NSCLC



- 57/71 (80%) NSCLC patients and 42/44 (95%) MTC patients had *RET* alterations detected at enrollment also confirmed in ctDNA at baseline. 37 MTC patients were included in the plot and 5 were excluded due to suspected germline *RET* variants
- At disease progression, selpercatinib continued suppressing variant allele frequency (VAF) of enrolling *RET* alterations in most NSCLC patients but not in MTC patients (median VAF change: -79% vs -6%; Wilcoxon Signed Rank test: p=0.015)

Conclusions

- Overall, acquired mechanisms of resistance were identified in 45% of ctDNA at the time of disease progression in the largest prospective dataset studying mechanisms of resistance to RET inhibition
- Mechanisms of resistance differ depending on tumor type
 - On target mechanisms of resistance were more common in MTC than NSCLC (43% vs 13%, respectively)
 - Bypass mechanisms of resistance (30%) included RAS/RAF activating alterations and potentially targetable *MET* amplifications
- Overall results suggest that *RET* was still a driver of progression for a large subset of MTC patients who might benefit from a second generation of RET inhibitor
- PD of most NSCLC patients was driven by non-RET-driven mechanisms which requires more comprehensive genetic testing to characterize
- More comprehensive strategies for testing may be needed to study the 55% of patients with unknown mechanisms of resistance and to optimally guide sequences of therapy and post-selpercatinib treatment strategies

Acknowledgements

Acknowledgements

- We would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible
- We would like to thank the trial investigators and study staff
- Medical writing support was provided James Hegarty of Eli Lilly and Company

Disclosures

Benjamin J Solomon has the following disclosures: Received compensation (institutional or personal) for speaker or advisory roles from AstraZeneca, Pfizer, Amgen, Roche-Genentech, Novartis, Merck, Bristol Myers Squibb, Eli Lilly and Company, Takeda, Janssen. Member of board of directors for Cancer Council of Victoria and Thoracic Oncology Group of Australasia. Received royalties from UpToDate. Served as a steering committee member for Roche-Genentech, Pfizer, Novartis.