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Treatment Sequencing and Outcomes in MET Exon 14 NSCLC: Clinicopathological Insights From the AURORA Registry (AURORA-MET)

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INTRODUCTION

- *MET*ex14 skipping occurs in ~3% of NSCLC and is targetable with selective MET TKIs[1]
- Optimal sequencing of MET TKIs and ICI-based therapies remains uncertain[2-5]
- We examined real-world treatment patterns and survival in *MET*ex14sk NSCLC

METHODS

- Retrospective analysis of *MET*ex14sk patients in the Australian AURORA cohort (ACTRN12625000038493)
- Compared 1L MET TKI versus ICI-based therapy
- Endpoints: PFS1, OS, progression patterns, and 2L treatment

RESULTS

Design:

- A total of 119 patients with *MET*ex14skip+ NSCLC were identified
- Of these, 80 received first-line (1L) MET TKI or immunotherapy-based therapy for advanced disease and were included in the analysis
- Cohort characteristics (Table 1), treatment patterns (Figure 1), and survival outcomes (Table 2; Figure 2) are presented
- Exploratory analysis using PD-L1 ≥80% cutoff (Table 2; Figure 3)

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Table 1: Cohort demographics and Outcomes by treatment received

	1L MET TKI N = 59 (%)	1L ICI ± CTx N = 21 (%)	1L ICI+CTx N = 15 (%)	1L ICI N = 6 (%)	Other N = 3 (%)
Age (years) Median (range)	77 (43,86)	67 (44,85)	65 (44,79)	72 (63,85)	80 (68, 81)
White/Caucasian	41 (69.5)	15 (71.4)	11 (73.3)	4 (66.7)	3 (100)
Asian	12 (20.3)	4 (19.1)	3 (20)	1 (16.7)	-
Other	6 (10.2)	2 (9.5)	1 (6.7)	1 (16.7)	-
Female	32 (54.2)	10 (47.6)	6 (40.0)	4 (66.7)	3 (100)
Male	27 (45.8)	11 (52.4)	9 (60)	2 (33.3)	-
Current/former smoker	32 (54.2)	14 (66.7)	10 (66.7)	4 (66.7)	2 (66.7)
Never smoker	27 (45.8)	7 (33.3)	5 (33.3)	2 (33.3)	1 (33.3)
ECOG					
0-1	51 (86.4)	18 (85.7)	13 (86.7)	5 (83.3)	3 (100)
≥2	2 (3.4)	1 (4.8)	1 (6.7)	-	-
Not available	6 (10.2)	2 (9.5)	1 (6.7)	1 (16.7)	-
CNS disease	7 (11.9)	1 (4.9)	1 (6.7)	-	1 (33.3)
≥3 sites of disease	21 (35.6)	5 (23.8)	4 (26.7)	1 (16.7)	1 (33.3)
Adenocarcinoma	45 (76.3)	14 (66.7)	9 (60.0)	5 (83.3)	3 (100)
Non-adenocarcinoma	14 (27.3)	7 (33.3)	6 (40)	1 (16.7)	
PD-L1					
<50%	35 (59.3)	14 (66.7)	13 (86.7)	1 (16.7)	3 (100)
<1%	18 (30.5)	7 (46.7)	7 (46.7)	-	3 (100)
1-49%	17 (28.8)	7 (40)	6 (40)	1 (16.7)	-
≥50%	24 (40.7)	7 (33.3)	2 (13.3)	5 (83.3)	-
50-79%	1 (1.7)	1 (4.8)	-	1 (16.7)	-
80-89%	15 (25.4)	4 (19.1)	2 (13.3)	2 (33.3)	-
≥90%	8 (13.6)	2 (9.5)	1 (6.7)	1 (16.7)	-
TP53 co-mutation					
Detected	10 (50)	1 (16.7)	1 (16.7)	-	-
Not detected	10 (50)	4 (66.7)	4 (66.7)	-	2 (66.7)
Unknown	39 (66.1)	16 (76.2)	10 (66.7)	6 (100)	1 (33.3)
Year 1L					
2015-2020	-	8 (38.31)	5 (33.3)	3 (50)	3 (100)
2021-2023	18 (30.5)	9 (42.9)	7 (46.7)	2 (33.3)	-
2024-2026	41 (69.5)	4 (19)	3 (20)	1 (16.7)	-
Progression	31 (52.6)	15 (71.4)	10 (66.7)	5 (83.3)	3 (100)
2L treatment	17 (28.8)	12 (57.1)	9 (60)	3 (50)	-
PFS1	15.7 (8.1, 23.1)	7.8 (3.6, 29.1)	7.8 (3.2, 29.1)	3.6 (2.0, NR)	7.79 (1.84,NR)
OS	26.8 (21.1,NR)	60.1 (41.4,NR)	57.9 (9.9,NR)	78.3 (14.7,NR)	20.5 (4.17,NR)

Figure 1: PD-L1 distribution by 1L treatment group

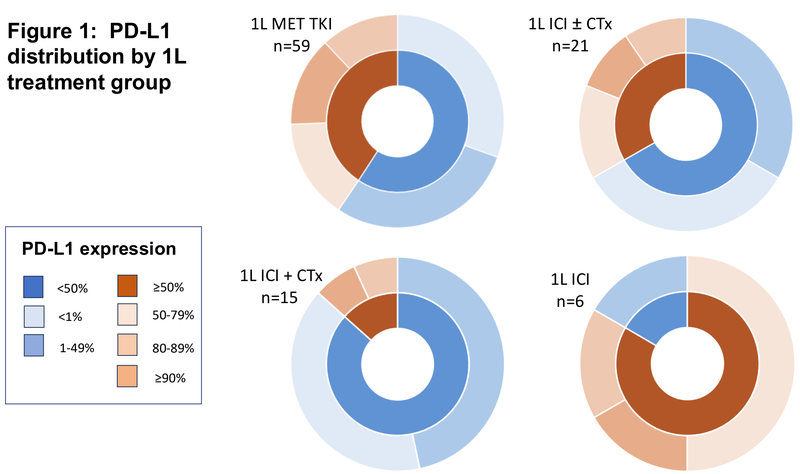


Figure 2: Kaplan-Meier Curves showing PFS1 and OS by 1L treatment

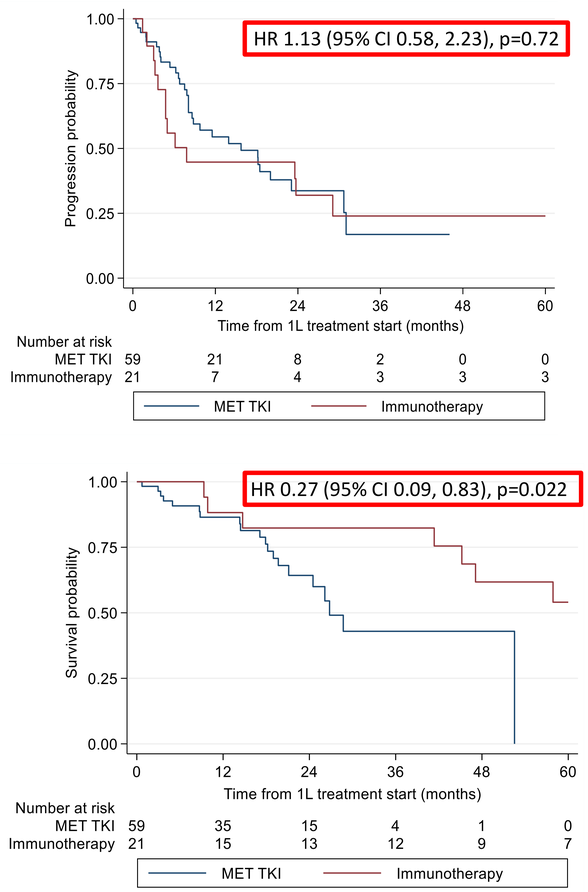


Table 2: PFS1/OS Multivariable Analysis

	PFS1 HR (95% CI)
1L ICI ± CTx vs MET TKI	1.13 (0.58,2.23) p=0.720
Non-adeno. vs adeno.	2.90 (1.54,5.44), p=0.001
≥3 sites vs <3 sites	1.96 (1.04,3.66) p=0.036
PD-L1 <80% vs ≥80%*	1.41 (0.72,2.77) p=0.321
	OS HR (95% CI)
1L ICI ± CTx vs MET TKI	0.27 (0.09,0.83) p=0.022
Non-adeno. vs adeno.	3.16 (1.45,6.90) p=0.004
≥3 sites vs <3 sites	1.42 (0.65,3.12) p=0.381
PD-L1 <80% vs ≥80%*	1.17 (0.48,2.84) p=0.733

Multivariable analysis, pre-defined primary model: MET TKI vs IO, histology and metastatic burden = 3 df.
* evaluated separately as an exploratory analysis by adding PD-L1 ≥80% to the primary model

Figure 3: Exploratory analysis of PFS and OS by PD-L1 <80% vs ≥80% and treatment group

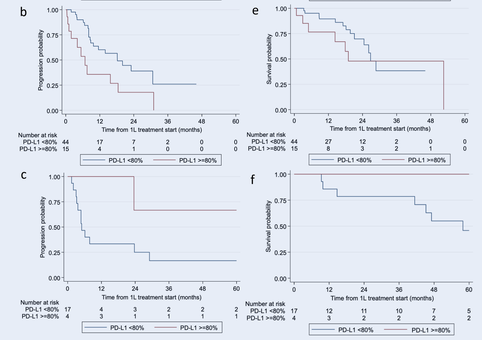


Figure 3: Exploratory analysis of PFS by a) PD-L1 <80% vs ≥80%, for b) 1L MET TKI, and c) 1L ICI, and d) OS by PD-L1 <80% vs ≥80% , for e) 1L MET TKI, and f) 1L ICI based treatment

DISCUSSION AND CONCLUSION

Actionable Take Away Message

In this real-world cohort

- Survival outcomes differed by 1L strategy despite similar PFS, with 1L ICI associated with longer OS
- These finding likely reflect treatment selection, limited subsequent therapy (only 28.8% from 1L TKI subgroup), and temporal confounding

Conclusions

- *MET*ex14skip+ NSCLC are a biologically and clinically heterogeneous disease, and there remains clinical equipoise in 1L treatment selection, with many not receiving 2L treatment

Future Direction for Research

- Prospective studies are needed to define optimal treatment sequencing and identify predictive biomarkers