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Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies

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ABSTRACT

Purpose The receptor tyrosine kinase rearranged during transfection (RET) can be oncogenically activated by gene fusions or point mutations. Multikinase inhibitors such as cabozantinib, lenvatinib and vandetanib have demonstrated activity in RET-dependent malignancies, and selective RET inhibitors (Selpercatinib and Pralsetinib) are in clinical trials. However, the responsiveness of RET-dependent malignancies to immune checkpoint inhibitors (ICIs) is unknown. We compared the time to treatment discontinuation (TTD) for ICI versus non-ICI therapy in patients with malignancies harbouring activating RET mutations or fusions (RET+).

Methods A retrospective review of all RET+ patients who were referred to the phase I clinical trials programme at the University of Texas MD Anderson Cancer Center was conducted. TTD was estimated using Kaplan-Meier analysis. Multivariate analysis using the Cox proportional hazard model was performed to identify independent risk factors of treatment discontinuation.

Results Of 70 patients who received systemic therapy for RET+ malignancies, 20 (28.6%) received ICI and 50 (71.4%) received non-ICI therapy. Non-ICI therapy was associated with decreased risk for treatment discontinuation compared with ICI in the overall population (HR=0.31; 95% CI 0.16–0.62; p=0.000834) and in patients with RET point mutations (HR=0.13; 95% CI 0.04–0.45; p=0.00134). In patients with RET fusions, non-ICI therapy was associated with a non-statistically significant decreased risk of treatment discontinuation (HR=0.59; 95% CI 0.25–1.4; p=0.24). ICI therapy and a diagnosis other than medullary thyroid cancer (MTC) were independent risk factors for treatment discontinuation.

Conclusion Our study supports the prioritisation of non-ICI over ICI therapy in patients with RET+ tumours.

key questions

What is already known about this subject?

► Immune checkpoint inhibitors (ICIs) are known to be inefficacious in EGFR and ALK aberrant non-small-cell lung cancer. The sensitivity of rearranged during transfection (RET)-aberrant malignancies to ICIs is unclear. Small retrospective studies of RET-aberrant non-small-cell lung cancer suggest inadequate efficacy of ICIs.

What does this study add?

► This is a large retrospective study comparing the efficacy of ICIs with non-immune checkpoint inhibitor therapy in RET-aberrant malignancies as measured by time to treatment discontinuation for disease progression. The study found that the risk of treatment discontinuation was significantly higher in RET-aberrant malignancies treated with ICIs compared with non-ICI therapy. On multivariate analysis, non-ICI therapy and non-medullary thyroid carcinoma diagnosis were independent risk factors for treatment discontinuation.

How might this impact on clinical practice?

► The findings of this study support prioritisation of non-ICI therapy over ICIs in RET-aberrant malignancies. This study was conducted prior to FDA-approval of the selective RET kinase inhibitors, selpercatinib and prasetinib. However, our findings add to the growing body of evidence regarding the role of ICIs in RET-aberrant malignancies.

INTRODUCTION

Aberrations in the receptor tyrosine kinase RET (rearranged during transfection), both activating point mutations and gene rearrangements, result in constitutive RET kinase activation and drive multiple malignancies, including medullary thyroid cancer (MTC) and lung cancer.[1–16] Multikinase inhibitors such as cabozantinib, lenvatinib and vandetanib non-selectively inhibit RET with modest activity in MTC with RET mutations[17–22] and in non-small-cell lung cancer (NSCLC) with RET fusions.[23–26] However, the benefit of multikinase inhibitors in RET-aberrant (RET+) malignancies is limited by significant toxicity.[21 22] The recent development of selective RET kinase inhibitors is poised

to alter the landscape of therapies for RET-aberrant malignancies.[27–32] In contrast, immune checkpoint inhibitors (ICIs) are Food and Drug Administration (FDA)-approved in a variety of malignancies with a response rate of 20%–30%.[33] The efficacy of ICIs in certain subsets of oncogene-driven NSCLC is limited.[34 35] However, their efficacy in NSCLC, MTC and other solid tumours driven by RET aberrations in comparison with multikinase inhibitors or systemic chemotherapy is uncertain. To determine whether there is a benefit of ICIs in RET+ malignancies, we performed a retrospective study comparing the time to treatment discontinuation (TTD) of ICI with non-ICI therapy among patients with RET+ malignancies.

METHODS

We conducted a retrospective review of all patients with RET+ malignancieswho were referred to the Department of Investigational Cancer Therapeutics, the phase I clinical trials programme at The University of Texas MD Anderson Cancer Center. The study was approved by MD Anderson's Institutional Review Board. Informed consent was waived due to the retrospective nature of the study. RET+ malignancy was defined as a tumour harbouring a known activating RET aberration (RET rearrangement or RET point mutations). Patients who did not receive any systemic therapy prior to referral and those who received selective RET kinase inhibitors were excluded from this analysis.

Baseline patient demographics, diagnosis, treatments received prior to referral, type of RET aberration and reason for treatment discontinuation were collected by a retrospective chart review. RET aberrations were detected by next-generation sequencing (NGS) methods as a part of routine clinical care from CLIA-certified laboratories (Oncomine, Thermo Fisher Scientific, Waltham, Massachusetts, USA; FoundationOne, Foundation Medicine, Cambridge, Massachusetts, USA; Guardant360, Guardant Health, Redwood City, California, USA). Information regarding programmed cell deathprotein ligand 1 (PD-L1) expression was collected if available from pathology reports. Tumour mutation burden (TMB) and microsatellite status were also collected if available from patients who underwent comprehensive NGS through FoundationOne.

TTD, defined as the time from treatment start to treatment discontinuation for disease progression or death, was chosen as the primary endpoint because of the variation in timing and modality of restaging imaging in the real-world setting prior to referral for phase I clinical trials.[36] TTD was analysed using the Kaplan-Meier method (JR, KRH). The R software packages 'survival' and 'survminer' were used for statistical analysis. Patients who discontinued treatment for reasons other than disease progression were censored. To identify independent predictors of TTD, multivariate analysis was performed using the Cox proportional hazard model.

RESULTS

Ninety-five patients with RET+ malignancies were referred to the MD Anderson phase I clinical trials programme between September 2014 and August 2018 (online supplemental figure 1). Twenty-five patients who had not received any systemic therapy prior to referral were excluded from this analysis. Of the 70 patients who had received systemic therapy, 20 (28.6%) had received ICI and 50 (71.4%) non-ICI therapy. Forty-five (64.3%) patients had discontinued treatment because of disease progression, 4 (5.7%) because of treatment completion and 16 (22.9%) patients because of toxicity (14 for non-ICI-related and 2 for ICI-related toxicity). Five patients remained on treatment at the time of referral.

Baseline patient characteristics are described in table 1. Thirty-four patients (48.6%) had RET fusions and 36 (51.4%) had RET point mutations. RET aberration was detected by tumour NGS in 47 (67.1%), fluorescent in situ hybridisation in 10 (14.3%), circulating cell–cell free DNA in 10 (14.3%), and unknown method in 3 (4.3%) patients. Sixty-four patients (91.4%) had somatic and 6 (8.6%) had germline RET aberrations. The online supplemental figure 2A and B shows specific RET aberrations, with M918T being the most common RET point mutation (66.7%) and *KIF5B* being the most common upstream fusion partner (41.2%). MTC (45.7%) was the most common diagnosis, followed by NSCLC (41.4%). All patients with MTC harboured RET point mutations. Among patients with NSCLC, 27 (93.1%) had RET fusions and 2 (6.9%) had RET point mutations. Among patients with NSCLC, 16 patients (55.2%) received ICI therapy, of which 14 had RET fusions and 2 had RET point mutations. Among patients with MTC, four (12.5%) received ICIs. All other patients received non-ICI therapies (online supplemental figure 3). The types of treatment received are listed in table 1. Multikinase inhibitors were the most common form of non-ICI therapy (64.0%), followed by systemic chemotherapy (26.0%), and anti-PD-1 antibody (60.0%) was the most common ICI therapy. Patients who received non-ICI therapy had a median of 0 prior lines of therapy (range 0–6), and patients who received ICI had a median of 1 prior line of therapy (range 0–6). Most patients (71.4%) had no tobacco exposure (current or former smoking). Among patients who received ICI and non-ICI therapies, 6 (30%) and 14 (28%) had tobacco exposure, respectively.

Overall, non-ICI therapy was associated with a longer median TTD compared with ICI (18.0 vs 5.2 months, p=0.00045) (Figure 1 A). A swimmer plot comparing the TTD of patients who received non-ICI and ICI therapies is displayed in Figure 2. Among the 36 patients with RET point mutations, non-ICI therapy was associated with a significantly longer median TTD compared with ICI therapy (31.9 vs 5.6 months, p=0.00016) (Figure 1B) (). Among the 34 patients with RET fusions, although the median TTD was longer in patients who received non-ICI therapy than in those who received ICI therapy,

Table 1 Baseline characteristics of the 70 patients with RET+ malignancies

Characteristics	n (%)	
	Non-ICI (N=50)	ICI (N=20)
Age, years, median (range)	57 (18-81)	59 (35-76)
Sex		
Female	27 (54.0)	9 (45.0)
Male	23 (46.0)	11 (55.0)
Ethnicity		
Caucasian	44 (88.0)	16 (80.0)
African American	3 (6.0)	0 (0.0)
Hispanic	3 (6.0)	1 (5.0)
Other	0 (0.0)	3 (15.0)
Tobacco exposure	14 (28.0)	6 (30.0)
Diagnosis		
Non-small-cell lung cancer	13(26.0)	16 (80.0)
Medullary thyroid cancer	28 (56.0)	4 (20.0)
Papillary thyroid cancer	4 (8.0)	0 (0.0)
Anaplastic thyroid cancer	1 (2.0)	0 (0.0)
Other	4 (8.0)	0 (0.0)
Origin of RET aberration		
Somatic	45 (90.0)	19 (95.0)
Germline	5 (10.0)	1 (5.0)
Type of RET aberration		
Fusion	20 (40.0)	14 (70.0)
Mutation	30 (60.0)	6 (30.0)
Median number of prior systemic therapies*	0 (0-6)	1 (0-6)
Treatment		
Chemotherapy	13 (26.0)	-
MKI	32 (64.0)	-
Arginase inhibitor	1 (2.0)	-
Chemotherapy+MKI	3 (6.0)	-
Osimertinib	1 (2.0)	-
Anti-CTLA-4	-	1 (5.0)
Anti-PD-1	-	12 (60.0)
Anti-PD-L1	-	3 (15.0)
Anti-PD-1+chemotherapy	-	3 (15.0)
Anti-PD-1+MKI	-	1 (5.0)

*Systemic therapies received prior to the most recent systemic therapy at the time of referral to MD Anderson Cancer Center
CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; MKI, multikinase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; RET, rearranged during transfection.

the difference was not statistically significant (8.3 vs 3.2 months, p=0.24) (Figure 1C) . Among the 29 patients with NSCLC, the median TTD was longer in patients who received non-ICI therapy, but the difference was not statistically significant (9.3 vs 3.4 months, p=0.16) (Figure 1 D) . On multivariate analysis, diagnosis (MTC vs non-MTC) and type of therapy (ICI vs non-ICI) were independent predictive factors of treatment discontinuation for disease progression (table 2). A non-MTC diagnosis was associated with a higher risk of treatment discontinuation compared with an MTC diagnosis (HR=2.67; 95% CI 1.29–5.51; p=0.0081), and non-ICI therapy was associated with a lower risk of treatment discontinuation compared with ICI therapy (HR=0.43; 95% CI 0.20–0.96; p=0.039)

PD-L1 expression, TMB and microsatellite status are described in table 3. The PD-L1 expression level was available in 18 patients, of which 15 (83.3%) had NSCLC. Overall, 4 patients (22.2%) had strong (≥50%), 4 (22.2%) had intermediate (1%–49%) and 10 (55.6%) had weak (<1%) PD-L1 expression by immunohistochemistry (IHC). All eight patients with strong and intermediate PD-L1 expression had NSCLC. Of the 10 patients with weak PD-L1 expression, 7 (70%) had NSCLC and 1 patient each had MTC, papillary thyroid cancer (PTC) and another cancer type. Two of the three patients with strong PD-L1 expression who received ICIs (one combination chemotherapy with an ICI and one pembrolizumab monotherapy) discontinued treatment because of disease progression within 2 months. The third patient with strong PD-L1 expression who received combination chemotherapy with ICI discontinued treatment because of toxicity at 0.7 months. One of the four patients with intermediate PD-L1 expression received combination chemotherapy with an ICI and had been on treatment for 1.4 months at the time of analysis without disease progression.

TMB data were available for 15 patients, of which 9 (60%) had NSCLC, 3 (20%) had MTC, 1 (6.7%) had PTC and 2 (13.3%) had other cancers. TMB was low (≤5/Mb) in all 15 patients. Microsatellite status was available for 10 patients, of which 5 (50%) had NSCLC, 1 (10%) had MTC, 1 (10%) had PTC and 3 (30%) had other cancers. All patients had microsatellite-stable tumours.

DISCUSSION

In this retrospective analysis, we found that patients with RET-aberrant malignancies who received non-ICI therapy were at a decreased risk of disease progression when compared with those who received ICIs. This is the largest study of real-world evidence comparing the efficacy of ICI versus non-ICI therapy in all RET-aberrant malignancies. As potent and highly selective RET tyrosine kinase inhibitors are under development, findings from this study are relevant to clinical decision making.

ICIs are currently US FDA-approved for the treatment of a variety of malignancies, including NSCLC. A retrospective analysis of 551 patients with oncogene-driven lung cancer who received ICIs included 16 patients with RET rearrangements.[37] For these patients, the median overall survival was 21.3 months (range 3.8–28), median progression-free survival (PFS) was 2.1 months (range 1.3–4.7), and only two patients had a long-term response.

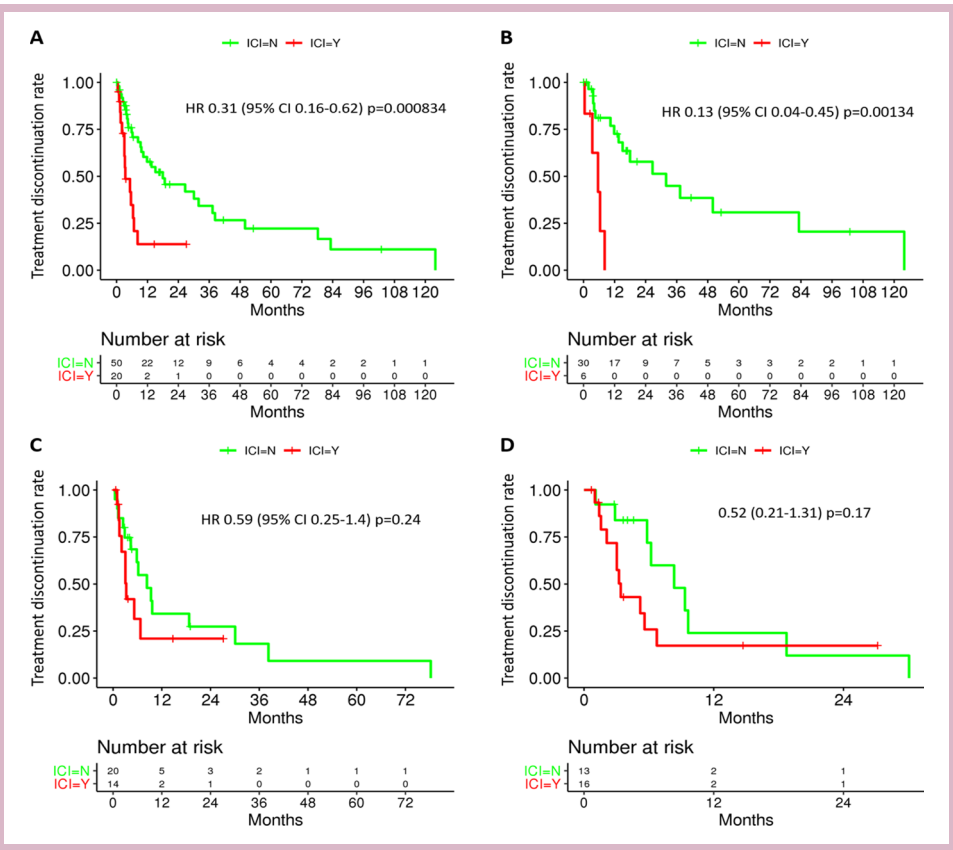

Figure 1 Time to treatment discontinuation A. Allpatients B. Patientswith RET point mutations C. Patientswith RET fusions D. Patientswith NSCLC. ICI, immune checkpoint inhibitor.

Our study included 70 patients with RET-aberrant malignancies and the TTD was significantly longer among patients who received non-ICI compared with ICI therapy (18 vs 5.2 months, p=0.00045).

The overall decreased risk of treatment discontinuation with non-ICI therapy could be attributed to the more indolent course of MTC because the majority of patients who received non-ICI therapy had MTC and most patients who received ICI therapy had NSCLC. However, on subgroup analysis, among patients with RET point mutations, most of whom had MTC, non-ICI therapy was associated with decreased risk of treatment discontinuation compared with ICIs. In patients with RET fusions, most of whom had NSCLC, non-ICI therapy was associated with a non-statistically significant decreased risk for treatment discontinuation compared with ICI therapy, which is in line with the findings of Offin *et al*.[38] Multivariate analysis showed that a non-MTC diagnosis was associated with increased risk of treatment discontinuation, once again highlighting the relatively indolent course of MTC irrespective of the type of therapy. However, non-ICI therapy was also independently associated with a decreased risk of treatment discontinuation. These findings suggest that both histological diagnosis and type of therapy independently influence the risk of disease progression in RET+ malignancies. The lack of statistically significant difference in TTD between the non-ICI and ICI arms among patients with NSCLC may be due to the use of older, less potent multikinase inhibitors. Patients who received highly potent and selective RET inhibitors were excluded from our study as trials are ongoing. These selective RET inhibitors have demonstrated promising clinical activity with limited toxicity. Thus, the treatment strategy for RET-aberrant malignancies may shift away from ICIs in the near future.

Where data were available, RET+ malignancies demonstrated low TMB and were microsatellite-stable. Among 15 patients with NSCLC whose PD-L1 status was known, 4 (26.7%) had a strong expression. Yet, the TTD was less than 2 months in two out of three patients with strong PD-L1 expression who received ICIs. Intrinsic induction of PD-L1 expression by oncogenes such as activating EGFR mutations or ALK fusions in NSCLC drive immune escape.[39–42] However, PD-L1 expression in oncogene-driven NSCLC is rarely accompanied by a high level of CD8+ TILs (tumor infiltrating lymphocytes), which are thought to be the main effectors of anti-PD-1/PD-L1 therapy.[35 43] This could explain low response rates to anti-PD-1/PD-L1 therapy in oncogene-driven NSCLC.

Although MTC patients who received ICIs had TTDs of up to 8.2 months, this duration was significantly lower than the median TTD of 31.9 months with multikinase inhibitor-based therapy among patients with RET point mutations in our study and lower than the PFS reported for vandetanib and cabozantinib in randomised phase III trials in MTC.[21 22] Our study lacks sufficient data regarding PD-L1 status and TMB

Table 2 Multivariate analysis of predictive variables for disease progression using the COX proportional hazard model

Predictor	HR (95% CI)	P value
Age*	0.99 (0.97–1.01)	0.37
Sex		
Female	Reference	
Male	1.45 (0.73–2.91)	0.29
Tobacco exposure		
No	Reference	
Yes	0.82 (0.39–1.70)	0.59
Diagnosis		
MTC	Reference	
Non-MTC	2.67 (1.29–5.51)	0.0081
Type of treatment		
ICI	Reference	
Non-ICI	0.43 (0.20–0.96)	0.039

*Continuous variable.
ICI, immune checkpoint inhibitor; MTC, medullary thyroid cancer.

of patients with MTC. However, other studies have demonstrated the non-immunogenic nature of MTCs. One retrospective study of 16 MTC patients showed that 94% of patients were PD-L1 negative with a paucity of TILs, which were also negative for PD-L1 expression in a majority of cases.[44] Another retrospective study of 87 MTC patients showed that only 22% of patients were PD-L1 positive (>1% by IHC, SP263), and 89.5% of these had weak to moderate staining intensity.[45] Hence, patients with MTC tend to have weak PD-L1 expression, low TMB and tend to be microsatellite-stable and therefore may not benefit from ICIs in comparison with non-ICI therapies.

Combination of chemotherapy and ICI has been FDA-approved for patients with NSCLC, including those with oncogenic drivers. In addition to direct cytotoxic effects, chemotherapeutic agents have been proposed to have a synergistic effect when combined with the anti-PD-1/PD-L1 blockade in NSCLC.[46] In our study, three patients received combined carboplatin, pemetrexed and pembrolizumab. One patient discontinued treatment because of toxicity at 0.7 months, one discontinued because of disease progression at 1 month, and one remained on treatment at 1.4 months without disease progression. The one MTC patient who received combined lenvatinib and pembrolizumab discontinued treatment at 0.4 months because of disease progression. Although ICIs may be used in combination with non-ICI therapies in patients with RET-aberrant malignancies, the benefit of adding ICI to non-ICI therapy needs to be studied.

Our study is limited by its retrospective nature, single-centre experience, lack of radiological assessments at prespecified intervals using RECIST criteria, and lack of centralised PD-L1

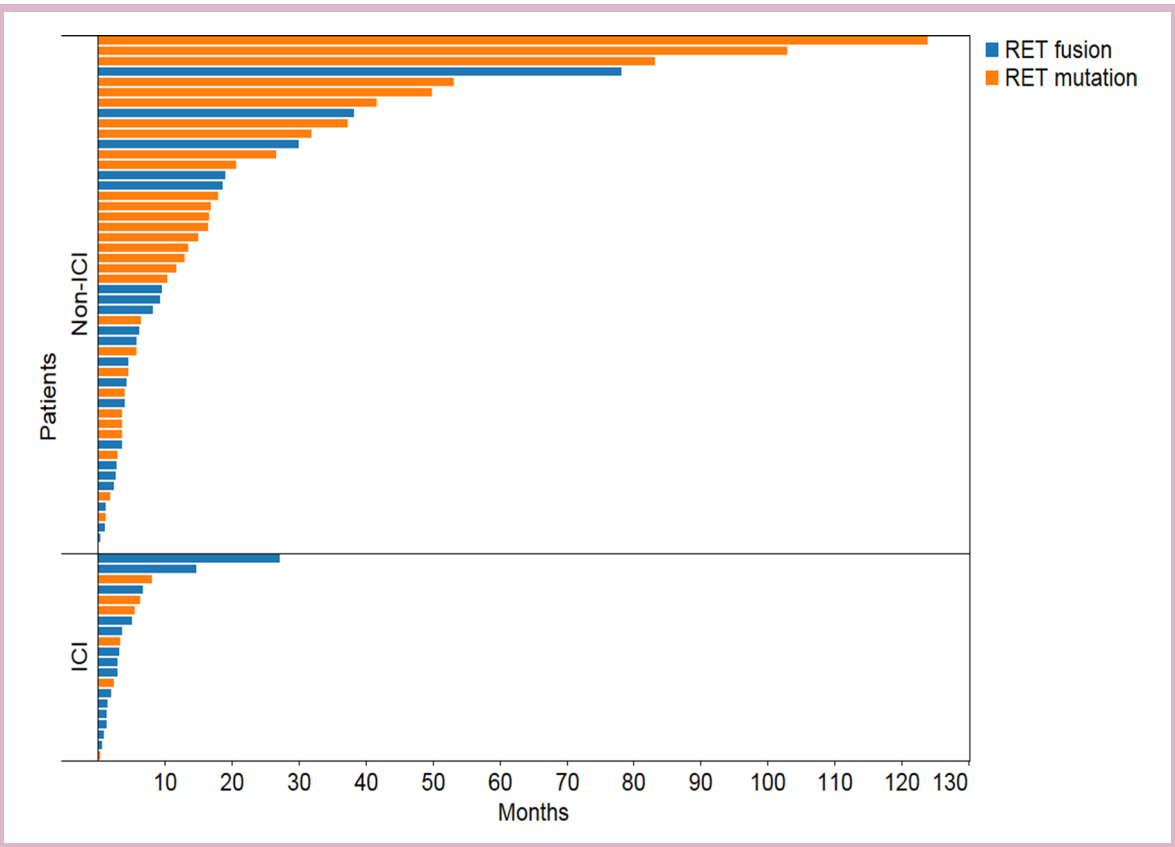

Figure 2 Time to treatment discontinuation swimmerplot. ICI, immune checkpoint inhibitor; RET, rearranged during transfection.

Table 3 PD-L1 expression, tumour mutation burden and microsatellite status for patients with available data, by diagnosis and type of therapy received

	n (%)	
PD-L1 expression	**Non-ICI (N=11)**	**ICI (N=7)**
Weak (<1%)		
NSCLC	4 (36.4)	3 (42.9)
MTC	1 (9.1)	0 (0.0)
PTC	1 (9.1)	0 (0.0)
Other	1 (9.1)	0 (0.0)
Intermediate (1%–49%)		
NSCLC	3 (27.3)	1 (14.2)
Strong (≥50%)		
NSCLC	1 (9.1)	3 (42.9)
Tumour mutation burden	**Non-ICI (N=7)**	**ICI (N=8)**
Low (≤5/Mb)		
NSCLC	3 (42.8)	6 (75.0)
MTC	1 (14.3)	2 (25.0)
PTC	1 (14.3)	0 (0.0)
Other	2 (28.6)	0 (0.0)
Microsatellite status	**Non-ICI (N=7)**	**ICI (N=3)**
Stable		
NSCLC	2 (28.6)	3 (100.0)
MTC	1 (14.3)	0 (0.0)
PTC	1 (14.3)	0 (0.0)
Other	3 (42.8)	0 (0.0)

ATC, anaplastic thyroid cancer; ICI, immune checkpoint inhibitor; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; PTC, papillary thyroid cancer.

and molecular testing. Although TTD is a pragmatic substitute for PFS in the real-world setting, PFS may not be an accurate indicator of efficacy in patients receiving ICIs. Additionally, our study does not report overall survival, which may be a better indicator of efficacy. This study was conducted prior to FDA-approval of the selective RET kinase inhibitors, selpercatinib and prasetinib. However, our findings add to the growing body of evidence regarding the role of ICIs in RET-aberrant malignancies.

In conclusion, our study supports the prioritisation of non-ICI over ICI therapies in patients with RET aberrations. Clinical trials evaluating the efficacy of ICIs in MTC (NCT03246958, NCT03072160) are ongoing. The selective RET inhibitor, selpercatinib, has received FDA-approval for the treatment of RET-fusion-positive NSCLC and thyroid cancer (radioactive iodine-refractory) as well as RET-mutant MTC.[29 47] Similarly, another selective RET inhibitor, pralsetinib, has received FDA approval for RET fusion positive NSCLC and was granted breakthrough designation by the FDA for RET-mutated MTC with no acceptable alternative treatments.[48 49] Randomized controlled trials comparing selpercatinib (NCT04194944) and pralsetinib (NCT04222972) to platinum doublet based regimen are ongoing. Other newer selective RET inhibitors such as BOS172738, TPX-0046 and TAS0953/HM06 are currently in clinical trials.[50 51] Until the results of these trials become available, we conclude that FDA-approved selective RET inhibitor, enrollment in selective RET inhibitor trials, initiation of multikinase inhibitors with RET activity or systemic chemotherapy should be prioritised over ICIs for the treatment of all RET-aberrant malignancies.

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