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ORIGINAL ARTICLE

Clinical outcomes of tumor-agnostic targeting of *BRAF*, tumor mutation burden-high, and *RET*

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Background: We report the BRAF p.V600E (BRAF V600E) mutations, high tumor mutational burden (TMB-H), and RET fusions frequency/outcomes with genomically matched therapies (GMTs). To raise awareness about GMTs providing data from a real-world scenario, the KISMET project was created. In this article we report the characteristics and the outcomes of patients with advanced cancer harboring three different classes of molecular alterations: BRAF V600E mutations, TMB-H, and RET fusions.

Patients and methods: We retrospectively assessed the prevalence of the three aforementioned agnostic targets among 10 893 patients who underwent next-generation sequencing (NGS) from February 2020 to May 2022. We evaluated the objective response rate (ORR), median progression-free survival (mPFS), and median overall survival (mOS) for GMT versus non-GMT in the three cohorts of patients with each specific alteration.

Results: BRAF V600E occurred in 6.5% (662/10 158) of patients, TMB-H in 11.2% (265/2369), and *RET* fusions in 0.6% (42/7105). GMT was given to 115 (72.3%) out of the 159 patients who started a new line of treatment after NGS testing: 65 of 85 with BRAF V600E mutations, 42 of 65 for TMB-H, and 8 of 9 for *RET* fusions. The ORR of GMT versus non-GMT was 55.6% versus 12.8% for all patients ($P < 0.0001$), 51% versus 17.6% for the BRAF V600E ($P = 0.016$), 57.6% versus 9.5% for the TMB-H ($P = 0.004$), and 75% versus 0% for *RET* fusions ($P = 0.30$). The mPFS for GMT versus non-GMT was 9.6 versus 3.7 months ($P = 0.001$), 9.2 versus 4.2 months ($P = 0.08$) for BRAF V600E, and 7.9 versus 3.7 months ($P = 0.04$) for TMB-H, respectively. For the eight patients with *RET* fusions who received RET inhibitors, the mPFS was 15.0 months.

Conclusions: BRAF V600E, TMB-H, and *RET* fusion were found in a wide variety of advanced cancers. Improved oncological outcomes with tumor type-agnostic GMT support the value of integrating comprehensive NGS testing and GMT administration for the aforementioned targets.

Key words: precision oncology, targeted therapies, real-world, *BRAF*, tumor mutational burden, *RET*

INTRODUCTION

The goal of precision oncology is to utilize therapies tailored to the individual molecular profile of each cancer patient.[1-6] Different techniques based on the biomarker, the sample, and cost considerations can assess the biomarkers predictive of a response to specific treatments. Next-Generation Sequencing (NGS), an extremely high-throughput sequencing technique of particular interest for biomarker testing, allows for simultaneous analysis of a large number of genes—including whole exome and genome—detecting alterations in DNA and/or RNA sequence with high analytical sensitivity and relatively low per-biomarker costs.[7] Recently, the United States Food and Drug Administration (FDA) has approved an increasing number of genomically matched oncology drugs—eight oncology drugs to date with biomarker-matched and tumor-agnostic indications. The rapid evolution of FDA tumor-agnostic oncology drug approvals makes physician awareness and patient access increasingly challenging and

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important to track. We created the Kismet program, the precision oncology real-world outcomes project, to address this and raise awareness of and improve precision oncology at the University of Texas MD Anderson Cancer Center and beyond. Currently nine agnostic FDA approvals exist, but this report is arbitrarily focused on patients with advanced solid tumors harboring BRAF V600E, tumor mutational burden-high (TMB-H, TMB $\geq$10 mut/Mb), or *RET* fusions. Real-world data on the remaining FDA-agnostic approvals will be reported in the future.

The RAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib was initially studied and FDA approved in *BRAF*-mutated melanoma.[8] Data from the ROAR trial and NCI-MATCH subprotocol H led to the FDA approval of this drug combination for BRAF V600E-mutated pretreated solid tumors in June 2022 excluding *BRAF*-mutated colorectal cancers, in which epidermal growth factor receptor inhibition was demonstrated to be necessary in combination with *BRAF*.[9-16] The KEYNOTE-158 trial results led to the June 2020 FDA approval of pembrolizumab, a humanized anti-programmed cell death protein 1 (PD-1) monoclonal antibody, for pretreated TMB-H advanced solid tumors.[17,18] *RET* fusions are rare alterations occurring in thyroid cancer, non-small-cell lung cancer (NSCLC), and other cancers.[19-28] Selpercatinib is a RET inhibitor recently approved by the FDA for pretreated advanced solid tumors harboring *RET* fusions on the basis of the LIBRETTO-001 trial, after being approved for NSCLCs and thyroid cancers with *RET* fusions and medullary thyroid cancer with *RET* mutations.[19,20,29,30]

In this article, we investigated the prevalence of BRAF V600E, TMB-H, and *RET* fusions across solid tumor types before analyzing and comparing respective clinical outcomes of genomically-matched therapies (GMTs) versus non-GMTs at a comprehensive cancer center.

PATIENTS AND METHODS

Patient selection

The University of Texas MD Anderson Cancer Center (MDACC) Institutional Review Board approved the KISMET retrospective study, protocol # 2020-1108, of advanced solid tumor patients (excluding melanomas and lymphomas) seen at MDACC from 1 February 2020 to 8 May 2022. Our analysis included evaluating the prevalence of patients with solid tumors with BRAF V600E mutations, TMB-H, or *RET* fusions by the Clinical Laboratory Improvement Amendments (CLIA)-certified molecular diagnostics laboratory tissue NGS testing at MDACC during the study period. We carried out outcome analysis in a subpopulation of patients using the following inclusionary criteria. We selected patients with advanced solid tumors who received a new line of treatment for advanced disease after the genomic test results with available follow-up data. This report excluded all patients with hematologic malignancies or multiple primary cancers. Furthermore, patients with melanoma and BRAF V600E were excluded from this study due to the well-characterized clinical benefit conferred by BRAF + MEK inhibitors in this population.

Testing for BRAF V600E mutation, TMB-H, and RET *fusion*

Institutional assays included matched tumor—normal DNA testing (146-610 genes) and amplicon-based tumor-only RNA fusion testing (51 genes), as described previously.[31,32] BRAF V600E results were available from all DNA-based tests. TMB quantification and DNA-based detection of *RET* fusions were only available from the 610-gene panel. The Precision Oncology Decision Support System at MDACC annotated the genomic testing results.[33] We collected the relevant clinical and molecular data of patients from electronic medical records. BRAF V600E mutation, TMB-H, or *RET* fusion systemic targeted treatments define GMT. In both the combined survival analysis population and in the three individual biomarker-positive subpopulations the clinical endpoints were analyzed.

Clinical outcome endpoints

Clinical endpoints analyzed included both the combined survival analysis population and the three subpopulations composed of TMB-H, BRAF V600E-mutated, and *RET* fusion patients. Study endpoints were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients who started GMT any time after NGS test results (GMT group) compared with non-GMT first-line therapy started after genomic test results (non-GMT group). The time from first cycle of therapy to disease progression or death from any cause, whichever occurred first, defined PFS. The time from first cycle of therapy to death from any cause defined OS.

The real-world RECIST v1.1, RANO, or PERCIST max criteria were used as appropriate for the restaging exams and the disease sites to calculate ORR.[34-36] We prioritized the RECIST 1.1 criteria to define the best response for a patient assessable with multiple criteria without any evidence of progressive disease (PD). ORR was defined as the percentage of complete responses (CRs) or partial responses (PRs) in patients treated after genomic test results with available radiological exams (baseline and $\geq$1 restaging before starting another line of treatment).[34] For PFS and best response calculation in the absence of restaging exams, the treating physician statement of clinical disease progression and subsequent permanent discontinuation of treatment was considered PD. For each applicable patient, dividing GMT PFS (PFS2) by the PFS of the immediate prior line of therapy (PFS1) calculated the PFS2/PFS1 ratio.[37,38] A PFS2/PFS1 ratio $\geq$1.3 defined patients with a GMT benefit. Survival analyses and the relative plots were carried out with RStudio and R v4.3.2 (packages: survminer, survival, ggplot2).

Statistical analyses

Descriptive statistics were used to analyze baseline characteristics of patients. Clinical and biological variables were categorized for patient age, previous lines of treatment, tumor types, and performance status (PS). Continuous variables were categorized. Categorical variables are

Table 1. Prevalence of BRAF V600E, TMB-H, and *RET* fusion

	BRAF V600E patients		TMB-H patients		*RET*-fusion patients	
	(*n*) Tested	(*n*) Mut.	(*n*) Tested	(*n*) TMB-H	(*n*) Tested	(*n*) Fusion
Total tested	10 158	242 (2.3)	2369	113 (4.7)	7105	14 (0.1)
Lip, oral cavity, and pharynx	327	0	6	1 (16.6)	210	0
Digestive organs	2653	62 (2.3)	788	33 (4.1)	2087	1 (0.1)
Appendix	70	5 (7.1)	26	2 (7.6)	61	0
Colorectal carcinoma	1274	48 (3.7)	427	21 (4.9)	1044	1 (0.1)
Small intestines	72	1 (1.3)	22	0	42	0
Pancreatic carcinoma	452	2 (0.4)	134	1 (0.7)	340	0
Cholangiocarcinoma	193	6 (3.1)	36	1 (2.7)	180	0
Respiratory system and intrathoracic organs	1743	9 (0.5)	14	1 (7.1)	1521	9 (0.6)
NSCLC squamous	194	0	2	1 (50)	170	0
NSCLC nonsquamous	1077	9 (0.8)	5	0	963	9 (0.9)
Skin	526	53 (10.0)	10	2 (20)	242	0
Melanoma	450	53 (11.7)	5	2 (40)	180	0
Squamous-cell carcinoma	8	0	1	0	4	0
Retroperitoneum and peritoneum	125	1 (0.8)	46	1 (2.1)	77	0
Connective and other soft tissues	168	0	19	0	81	0
Breast	953	3 (0.3)	212	13 (6.1)	450	0
Invasive ductal carcinoma	745	1 (0.1)	171	8 (4.6)	347	0
Invasive lobular carcinoma	98	1 (1.0)	26	5 (19.2)	55	0
Female genital organs	1067	0	384	11 (2.8)	515	0
Vulva	22	0	6	0	9	0
Cervix	119	0	35	4 (11.4)	43	0
Corpus uteri	370	0	147	6 (4.0)	197	0
Ovary	438	0	165	1 (0.6)	213	0
Urinary tract	1212	1 (0.0)	516	36 (6.9)	773	1 (0.1)
Penis	9	0	4	1 (25)	5	0
Prostate gland	651	0	296	12 (4.0)	355	0
Kidney	222	0	74	1 (1.3)	153	0
Renal pelvis	44	0	23	5 (21.7)	35	0
Ureter	28	0	11	0	20	0
Bladder	211	1 (0.4)	86	18 (20.9)	168	0
Other and unspecified urinary organs	39	0	20	1 (5)	30	1 (3.3)
Other parts of the central nervous system	775	18 (2.3)	243	8 (3.2)	659	0
Brain	678	17 (2.5)	219	8 (3.6)	604	0
GBM	382	8 (2.0)	114	4 (3.5)	349	0
Astrocytoma	148	3 (2.0)	46	2 (4.3)	132	0
Glioma	80	5 (6.2)	31	1 (3.2)	64	0
Thyroid and other endocrine glands	340	76 (22.3)	87	1 (1.1)	298	3 (1.0)
Papillary	120	62 (51.6)	34	0	124	3 (2.4)
Anaplastic	67	14 (20.8)	17	1 (5.8)	55	0
Unknown primary site	269	19 (7.0)	44	6 (13.6)	192	0

Prevalence of BRAF V600E mutations, TMB-H, and *RET* fusion across solid cancers in a cohort of 10 158, 2369, and 7105 sequenced cases, respectively. All sequenced cases were extracted from the KISMET project (accessed on 8 May 2022). The data is *n*, %.
GBM, glioblastoma multiforme; NSCLC, non-small-cell lung cancer; TMB-H; tumor mutational burden-high (≥10 mutations/megabase).

displayed as numbers and percentages (%) and were compared using the chi-square test or Fisher's exact test, as appropriate for case count.

Survival was calculated using the Kaplan—Meier (KM) method and the log-rank test was used to compare the survival distribution between patients who received GMT versus non-GMT in the combined survival population and in the three biomarker-defined subpopulations. The Cox proportional hazards model was used to estimate the association of independent factors with survival time (PFS and OS) in multivariable analysis. Hazard ratio (HR) and confidence intervals (CI) were reported. The multivariable analysis for OS and PFS included treatment received (GMT versus non-GMT), age (<60 years versus ≥60 years), number of previous lines of therapy (<3 versus ≥3), Eastern Cooperative Oncology Group (ECOG) PS (≥2 versus <2), primary tumor type (only tumors with a case count of at least five were categorized separately), and having received a previous GMT as covariables.

Two-sided $P < 0.05$ was considered significant. Statistical analyses were carried out with RStudio and R v4.3.2.

RESULTS

Prevalence of BRAF V600E, TMB-H, and *RET* fusions

A total of 10 893 patients with advanced solid tumors across 333 distinct diagnoses received NGS testing. Of these, 10 158, 2369, and 7105 patients were tested on platforms that could detect BRAF V600E mutation, TMB-H, or *RET* fusions, respectively. A total of 662 (6.5%) patients were positive for BRAF V600E mutation, 265 (11.2%) for TMB-H, and 42 (0.6%) had a *RET* fusion. Table 1 and Figure 1 summarize the prevalence of genomic alterations across tumor types.

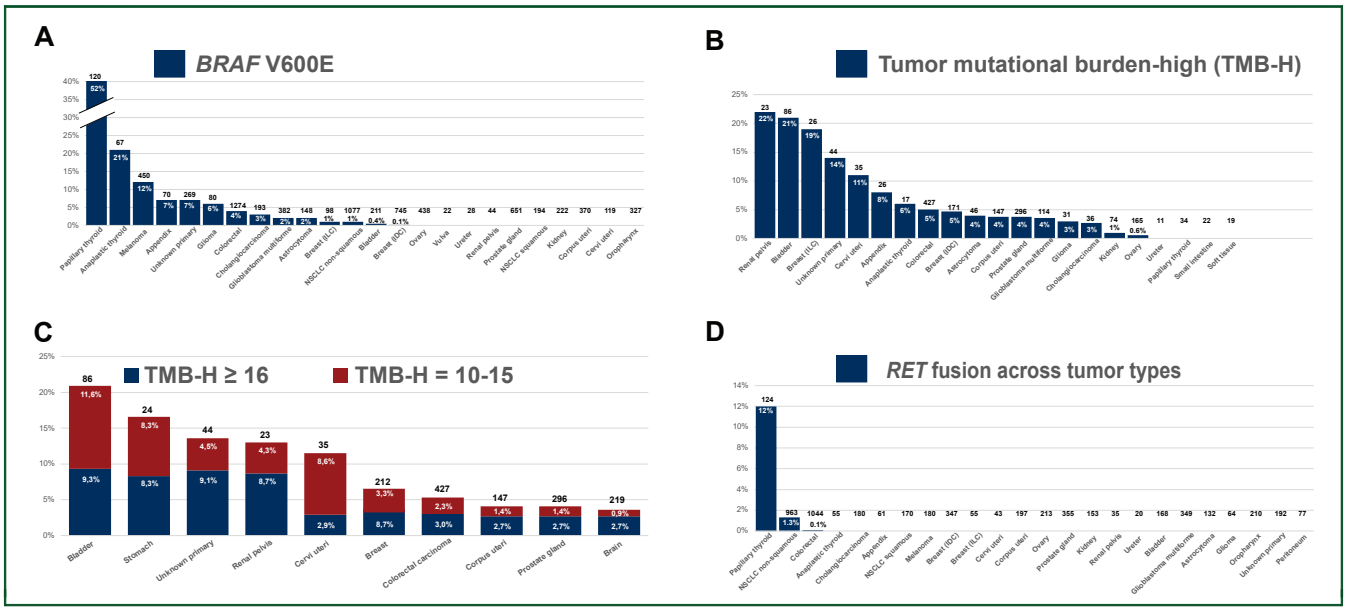

Figure 1. Prevalence of BRAF V600E, TMB-H, or *RET* fusion across tumor types. (A) Prevalence of BRAF V600E mutations across cancer types in a cohort of 10 158 sequenced cases. (B) Prevalence of TMB-H or (C) TMB 10-15 versus ≥16 across cancer types in a cohort of 2369 sequenced cases using a panel that reports TMB. This NGS assay was not used for lung cancer and melanoma testing during this study interval. (D) Prevalence of *RET* Fusion across diverse cancer types in a cohort of 7105 sequenced cases using fusion panels. Numbers above the bar graph are total patients tested. The percentages (inside bar graphs) are the proportion of total patients tested with the genomic alteration. NSCLC non-small-cell lung cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NGS, next generation sequencing; TMB-H, tumor mutational burden-high.

BRAF V600E prevalence

BRAF V600E was detected in multiple cancer types. Two hundred and forty-two patients with a BRAF V600E mutation fulfilled the study criteria and were included in the study. The most commonly represented tumor types were endocrine cancers (76/340, 22.3%) including 62 papillary thyroid carcinomas (PTCs) and 14 anaplastic thyroid carcinomas, carcinoma of unknown primary (CUP) (19/269, 7.0%), and skin cancers, all of which were melanomas (53, 11.7%) (Table 1, Figure 1A). PTCs had the highest prevalence (62/120, 51.6%). Ninety-seven out of the 184 patients with non-melanoma *BRAF*-mutant solid tumors (52.7%) received GMT. Forty patients (41.2%) received a GMT for an FDA-approved indication at the time of treatment, whereas GMT was administered to 41 patients (42.3%) off-label and 16 patients (16.5%) in the context of a clinical trial (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105061). Notably, the majority of off-label treatments were BRAF inhibitors for *BRAF*-mutant cancers based on the results reported at academic meetings or publications.

Survival analysis included 85 patients who started a new line of treatment after comprehensive NGS test results: 65 GMT (any BRAF inhibitor) and 20 non-GMT (Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2025.105061).

TMB-H prevalence

One hundred and fifty-two patients (70 outside NGS, 7 multiple cancers, 75 early disease) were excluded, resulting in 113 (4.7%) patients with TMB-H advanced solid tumors identified by institutional NGS. Of the 2369 patients who had TMB assessed, 113 (4.8%) were TMB-H (TMB ≥10). The most frequent TMB-H tumors were CUPs (6/44, 13.6%), urinary tract tumors (36/516, 6.9%), and invasive breast cancers (13/197, 6.1%) (see Table 1 and Figure 1B for the prevalence of TMB-H across tumor types). As some studies have explored a higher threshold of TMB ≥16,[39] we identified the proportion of patients having TMB-H ≥16 in the survival analysis using this alternative cut-off (Figure 1C).

Forty-two (37.1%) received GMT (defined as a PD-1/programmed death-ligand 1 inhibitor), with 37 (88.1%), 3 (7.1%), and 2 (4.7%) via FDA-approved indication at that time, off-label use, or a part of a clinical trial, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105061).

Excluding an additional 48 patients (6 lost to follow-up and 42 did not start therapy after genomic testing) led to the survival analysis of 65 patients: 42 anti-PD(L)1 (GMT, 36 assessable for response, 14 assessable for PFS2/PFS1) plus 23 patients who received GMT (21 assessable for response, Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2025.105061).

RET fusion prevalence

Of the 7105 patients assessed, 42 (0.6%) were positive for *RET* fusions (Figure 1D). Of nine patients who were eligible for assessment of clinical outcomes, eight (57.1%) received GMT of which six were for an FDA-approved indication and two were part of a clinical trial, respectively (Supplementary Table S1, Supplementary Figure S1C, available at https://doi.org/10.1016/j.esmoop.2025.105061).

Table 2. Patient characteristics

		BRAF V600E		*P* value		TMB-high		*P* value		RET fusion		*P* value
		BRAFi ($n = 65$)	Other therapy ($n = 20$)			Anti-PD-(L)1 ($n = 42$)	Other therapy ($n = 23$)			RETi ($n = 8$)	Other therapy ($n = 1$)	
Sex, *n* (%)	Female	29 (44.6)	13 (65.0)	0.1108[a]	Female	19 (45.2)	8 (34.8)	0.4134[a]	Female	7 (87.5)	0 (0)	0.2222[b]
	Male	36 (55.4)	7 (35.0)		Male	23 (54.8)	15 (65.2)		Male	1 (12.5)	1 (100.00)	
Ethnicity, *n* (%)	Asian	2 (3.1)	2 (10.0%)	0.7460[b]	Asian	2 (4.8)	1 (4.3)	0.0799[b]	Asian	2 (25.0)	0 (0)	1.0000[b]
	Black or African American	3 (4.6)	0 (0)		Black or African American	0 (0)	3 (13.0)		Black or African American	1 (12.5)	0 (0)	
	Declined to answer	1 (1.5)	0 (0)		Declined to answer	0 (0)	0 (0)		Declined to answer	0 (0)	0 (0)	
	Hispanic or Latino	7 (10.8)	1 (5.0)		Hispanic or Latino	0 (0)	0 (0)		Hispanic or Latino	1 (12.5)	0 (0)	
	Other	12 (1.5)	0 (0)		Other	0 (0)	0 (0)		Other	0 (0)	0 (0)	
	White or Caucasian	50 (76.9)	17 (85.0)		White or Caucasian	40 (95.2)	19 (82.6)		White or Caucasian	4 (50.0)	1 (100.00)	
TMB class, *n* (%)		—	—		TMB $\geq$ 16	31 (73.8)	7 (30.4)	0.0007[a]		—	—	
		—	—		TMB 10-15	11 (26.2)	16 (69.6)			—	—	
Age, years, *n* (%)	<60	25 (38.5)	7 (35.0)	0.7799[a]	<60	7 (16.7)	9 (39.1)	0.0444[a]	<60	5 (62.5)	0 (0)	0.4444[b]
	>60	40 (61.5)	13 (65.0)		>60	35 (83.3)	14 (60.9)		>60	3 (37.5)	1 (100.00)	
Number of previous lines for advanced disease, *n* (%)	<3	60 (92.3)	17 (8%)	0.5782[b]	<3	32 (76.2)	14 (60.9)	0.1941[a]	<3	8 (100.0)	1 (100.00)	
	≥3	5 (7.7)	3 (15.0)		≥3	10 (23.8)	9 (39.1)		≥3	0 (0)	0 (0)	
Tumor types[c], *n* (%)	Brain/CNS cancer	8 (12.3)	0 (0)	0.0040[b]	Breast cancer	4 (9.5)	5 (21.7)	0.0082[b]	Colorectal adenocarcinoma	1 (12.5)	0 (0)	0.2222[b]
	Cholangiocarcinoma	4 (6.2)	1 (5.0)		Colorectal adenocarcinoma	1 (2.4)	4 (17.4)		NSCLC	7 (87.5)	0 (0)	
	Colorectal adenocarcinoma	14 (21.5)	11 (55.0)		Other	17 (40.5)	5 (21.7)		Urothelial Carcinoma	0 (0)	1 (100.00)	
	NSCLC	4 (6.2)	2 (10.0)		Prostate adenocarcinoma	4 (9.5)	6 (26.1)					
	Other	6 (9.2)	4 (20.0)		Urothelial carcinoma	16 (38.11)	3 (13.0)					
	Thyroid	29 (44.6)	2 (10.0)									
Brain metastases, *n* (%)	No	62 (95.4)	18 (90.0)	0.5872[b]	No	37 (88.1)	18 (78.3)	0.3068[b]	No	6 (75.0)	1 (100.00)	1.0000[b]
	Yes	3 (4.4)	2 (10.0)		Yes	5 (11.9)	5 (21.7)		Yes	2 (25.0)	0 (0)	
PS_class, *n* (%)	<2	54 (83.1)	17 (85.0)	1.0000[b]	<2	38 (90.5)	21 (91.3)	1.0000[b]	<2	8 (100.0)	1 (100.0)	—
	≥2	11 (16.9)	3 (15.0)		≥2	4 (9.5)	2 (8.7)		≥2	0 (0)	0 (0)	

TMB-H, tumor mutational burden-high [≥10 mutations/megabase (mut/Mb)].
[a]Pearson's chi-square test.
[b]Fisher's exact test.
[c]For *BRAF* and TMB-H, only tumors with at least five cases are reported separately.

https://doi.org/10.1016/j.esmoop.2025.105061

Table 3. Patient responses

		BRAF V600		*P* value	TMB-H		*P* value	RET fusion		*P* value
		BRAFi ($n = 49$)	Other ($n = 17$)		Anti-PD-(L)1[a] ($n = 33$)	Other ($n = 21$)		RETi ($n = 8$)	Other ($n = 1$)	
Best response, *n* (%)	CR	3 (6.1)	1 (5.9)	0.0624[a]	1 (3.0)	0 (0.0)	0.0018[a]	3 (37.5)	0 (0.0)	0.1111[a]
	PR	22 (44.9)	2 (11.8)		18 (54.5)	2 (9.5)		3 (37.5)	0 (0.0)	
	SD	14 (28.6)	8 (47.1)		5 (15.1)	9 (42.9)		2 (25.0)	0 (0.0)	
	PD	10 (20.4)	6 (35.3)		9 (27.3)	10 (47.6)		0 (0.0)	1 (100.0)	
OR, *n* (%)	No	24 (49.0)	14 (82.4)	0.02[b]	14 (42.4)	19 (90.5)	0.0004[b]	2 (25.0)	1 (100.0)	0.3333[a]
	Yes	25 (51.0)	3 (17.6)		19 (57.6)	2 (9.5)		6 (75.0)	0 (0)	

CR, complete response; OR, objective response; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.
[a]Fisher's exact test for count data.
[b]Pearson's chi-square test.

Characteristics of patients who received GMT versus non-GMT

In total, 159 patients were included in the survival analysis: 115 in the GMT group (3 were not assessable for PFS in the BRAF V600E cohort) and 44 in the non-GMT group.

With regard to TMB analysis, TMB $\geq$16 was more frequent in the GMT group (31/42 patients, 73.8%) versus the non-GMT group (7/23 patients, 30.4%, $P < 0.001$). The GMT and non-GMT patients also differed by age class, ECOG PS, and tumor types in the TMB-H cohort, and tumor types in the BRAF cohort (Table 2).

Regarding TMB-H, 32/42 (76.2%) of the GMT and 14/23 (60.9%) of the non-GMT group received less than three previous lines of therapy; all the nine *RET* fusion-positive advanced solid tumor patients included in the survival analysis received less than three previous lines of therapy (Table 2). The median number of previous lines of therapy for advanced disease in the TMB-H cohort was 1 versus 2, in BRAF cohort was 1 versus 0, and in the *RET* cohort was 0 versus 0 for the GMT and non-GMT groups, respectively. Seven out of the eight patients who received *RET* inhibitors had NSCLC, and one had colorectal carcinoma.

GMT versus non-GMT response to treatment

Overall, 129 patients were assessable for the evaluation of ORR, which was higher in the GMT group (50/90, 55.6%) as compared with the non-GMT group (5/39, 12.8%, $P < 0.0001$). The ORR of GMT versus non-GMT was 55.6% versus 12.8% ($P < 0.0001$). The ORR was 51% versus 17.6% for the BRAF V600E ($P = 0.016$), 57.6% versus 9.5% for the TMB-H ($P = 0.004$), and 75% versus 0% for *RET* fusions ($P = 0.30$). Notably in the *RET* fusion cohort, eight of nine patients received GMT, and six out of eight patients who received GMT responded to treatment with three CRs (Table 3).

Univariable survival analysis for GMT versus non-GMT

For the patients with all three genomic alterations, the mPFS was longer for the GMT (9.6 months, 95% CI 7.3-14.0 months) versus the non-GMT group (3.7 months, 95% CI 2.8-6.8 months, $P = 0.001$, HR 0.51, 95% CI 0.34-0.77). The median overall survival (mOS) did not differ significantly [GMT: 24 months, 95% CI 19 months-not evaluable (NE); non-GMT: 16 months, 95% CI 12 months-NE; HR 0.72, 95% CI 0.42-1.23, $P = 0.23$, Figure 2A and B].

In the BRAF V600E cohort, the mPFS showed a favorable trend for the GMT ($n = 62$, median 9.2 months, 95% CI 5.8-17.0 months) versus the non-GMT group ($n = 20$, median 4.2 months, 95% CI 2.3 months-NE, $P = 0.076$, HR 0.59, 95% CI 0.33-1.06). There were no significant differences in the mOS (GMT: median 19 months, 95% CI 15-25 months; non-GMT median 12 months, 95% CI 4.8 months-NE, $P = 0.8$, HR 0.62, 95% CI 0.31-1.24, Figure 2E and F).

In the TMB-H cohort, the PFS was superior for the GMT ($n = 42$, median 7.9 months, 95% CI 2.6 months-NE) versus non-GMT patients ($n = 23$, 3.7 months, 95% CI 2.8-7.8 months, $P = 0.04$, HR 0.54, 95% CI 0.30-0.98). There were

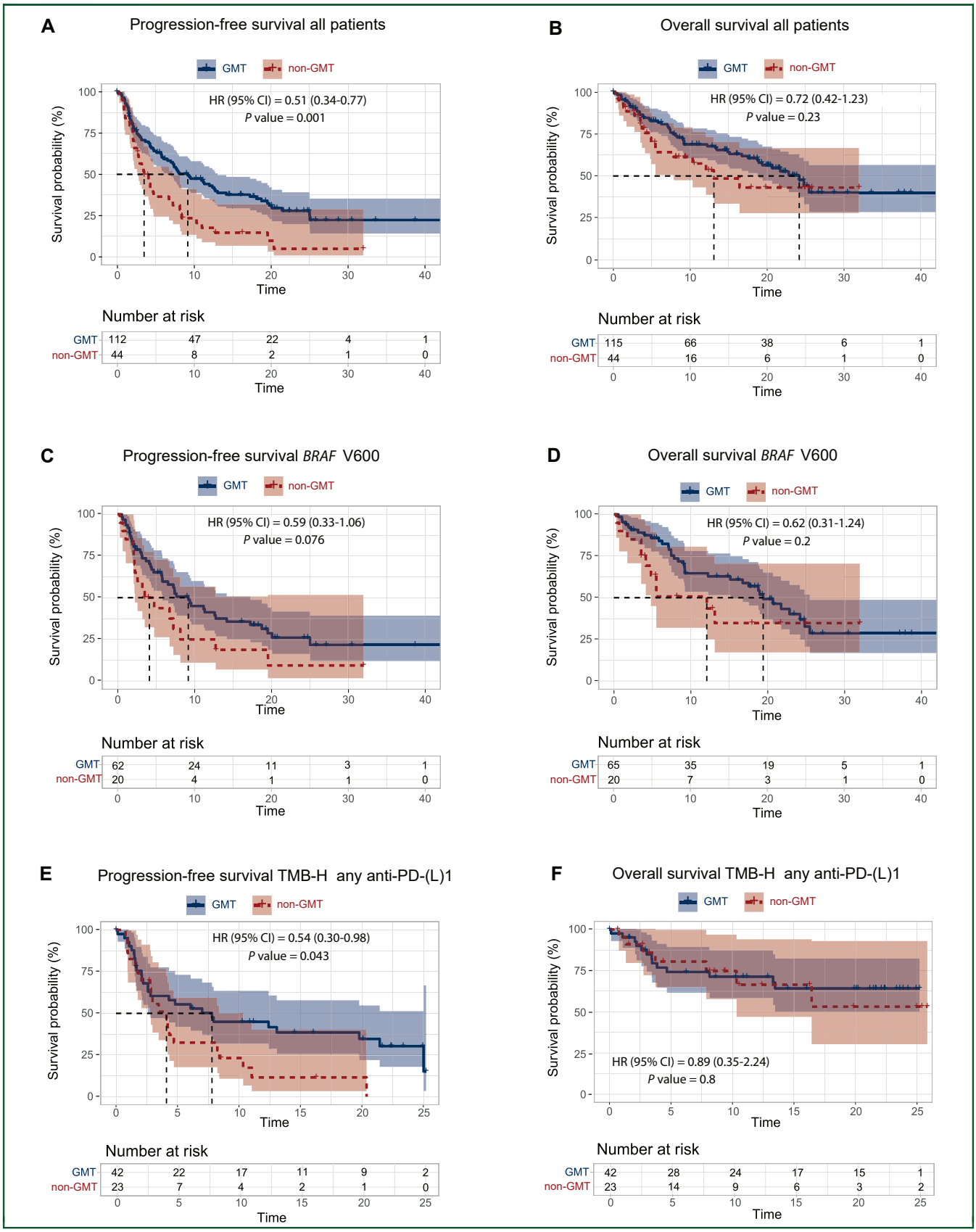

Figure 2. Kaplan–Meier curves for median progression-free survival (mPFS) and median overall survival (mOS) curves of patients with genotype-matched therapies (GMT) and without (non-GMT); mPFS (A) and OS (B) for patients with tumors positive for all GMT patients (BRAF V600E, TMB-H, and *RET* fusion combined) versus non-GMT; mPFS (C) and mOS (D) for patients with tumors positive for BRAF V600E; and mPFS (E) and mOS (F) for patients with tumors positive for TMB-H.

CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TMB-H, tumor mutational burden-high.

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no significant differences observed in OS and the mOS was not reached ($P = 0.8$, Figure 2C and D).

In the *RET* fusion cohort, the mPFS was 15 months (95% CI 11 months-NE) for GMT. The mOS was not reached in the GMT group ($n = 8$). The comparison between GMT and non-GMT for the *RET* fusion cohort was not meaningful as there was only one patient in the non-GMT group (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105061).

Survival analysis—multivariable survival analysis of GMT versus non-GMT

In the multivariable analysis across biomarkers, the improved PFS with GMT was lost when adjusting for the covariables ($P = 0.09$). As expected, ECOG PS ≥ 2 and being heavily pretreated (three or more previous lines of therapy for advanced disease) were consistently associated with worse survival outcomes when adjusting for age (<60 or ≥ 60 years), primary tumor, and TMB value (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105061).

We included in the multivariable analysis the previous exposure to a drug targeting the same molecular alteration in the *BRAF* and TMB-H cohorts. Twelve and nine patients had previously received an anti-BRAF and an anti-PD-(L)1 agent, respectively. None of the patients in the *RET* fusion cohort were previously exposed to *RET* inhibitors. Previous GMT administration was independently associated with unfavorable PFS in the TMB-H cohort (HR 3.01, 95% CI 1.03-8.81, $P = 0.04$), while a not statistically significant trend toward worse PFS and OS was detected in the *BRAF* cohort or when considering the patients of all the three cohorts together (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105061).

PFS2/PFS1 ratio

Patients who had received GMT and PFS on a prior line of evaluable therapy were considered assessable for PFS2/PFS1. Thirty patients were assessable in the BRAF V600E cohort, with 16 patients (53.3%) having a ratio ≥ 1.3. In TMB-H cohort, 7 out of 14 assessable patients (50%) had a PFS2/PFS1 ratio ≥ 1.3. A total of three patients were assessable in the *RET* fusion cohort with one patient (33.3%) having a ratio ≥ 1.3.

DISCUSSION

Although there is great interest in the development of tumor-agnostic therapies, the activity of such agents is often difficult to discern due to variable standards of care and expected PFS for different diseases. In this study we have trawled through a large cohort of 10 893 patients with solid tumors accounting for 333 distinct diagnoses. We report the frequency of three targets for tumor-agnostic therapies recently approved and report the experience with GMT in a comprehensive cancer center.

We described how the prevalence of BRAF V600E mutation (6.5%) is consistent with the prevalence of 7% across 2000 patients with various tumors types reported by our group in earlier series[40] and by others.[41] Our frequency of TMB-H found across various solid tumor types (4.7%) is comparable to a previously reported prevalence.[42-45] RET alterations were rare, and our prevalence of *RET* fusions was the highest among those in PTC (2.4%) and NSCLCs (0.9%), and this is also consistent with previous reports.[46] Notably, we report profiling on an NGS platform that was launched in our institution for selected tumor types, with few patients with lung cancer and melanoma profiled, thus potentially decreasing their representation in the series.

Our results are relevant to evaluate the impact of broad NGS testing and to grant patients with cancer access to targeted treatments with high actionability evidence. Overall, 115 out of the 159 patients (72.3%) who started a treatment after the results of genomic testing received GMT, suggesting that NGS changed the treatment plan of a high proportion of patients with these high value targets.

Moreover, our study demonstrated the effectiveness of targeting BRAF V600*E* mutations, TMB-H, and *RET* fusions in a real-world scenario. The ORR in BRAF V600E-mutant tumors was 51%, similar to what was demonstrated in the ROAR trial,[13] ranging from 0% to 89% in *BRAF*-mutated rare cancers. The mPFS in our study was 9.2 months, and was comparable to the mPFS reported by the ROAR trial (5.5-9.5 months, depending on the tumor type).

On the other hand, our study showed an ORR higher than previously reported in a selected group of patients with TMB-H (57.6%), as compared with the exploratory biomarker analysis of the KEYNOTE-158 trial leading to the FDA-agnostic approval of pembrolizumab, in which the ORR was 29% among TMB-H patients.[17] The proportion of patients showing a shrinkage of the tumor in KEYNOTE-158 was 58%, and the difference with our results may be explained by the different criteria employed. In KEYNOTE-158, the ORR was assessed by RECIST 1.1 criteria, while, due to the real-world nature of our study, we used RECIST 1.1, PERCISTmax, or RANO. It is reasonable that patients having a tumor reduction not matching the RECIST 1.1 criteria in KEYNOTE-158 may have matched PERCISTmax criteria for metabolic response. A real-world experience by Palmeri et al. published in 2022 assessing the utility of TMB-H and microsatellite instability as biomarkers for immunotherapy showed an ORR of 55.9% and an mPFS of 24.2 months, longer than the 7.9 months in our analysis.[47] This finding may rely on the 20 mut/MB cut-off used for defining TMB-H patients, as the TMB value was linearly associated with tumor response and then potentially with longer PFS.[48]

Despite the small number of patients with *RET* fusions included in our survival analysis, the ORR was remarkable (75%) and did not differ significantly from the results of the LIBRETTO-001 trial when referring to patients with NSCLC (ORR 61%). Further, the responses were durable, highlighting the importance of being aware of this rare but important target.

Our study has several limitations that might limit the generalizability of our findings. Our cohort was heterogeneous,

and some of the patients were treated in clinical trials with strict eligibility criteria, while others were treated off-label or on standard of care, necessitating a retrospective review of the imaging of response assessment. Although NGS is a powerful tool for discovery, tumor heterogeneity and low tumor purity specimens may result in false-negative results.[49] Further, only *RET* fusions that were targeted in the amplicon-based RNA NGS assay would be detected, potentially excluding other *RET* fusion types. Therefore, we may be underestimating the frequency of genomic alterations. The institutional NGS assays that assessed TMB were not deployed in the melanoma or thoracic care centers until the latter part of the study period underestimating the number of melanomas or NSCLCs that were tested. Furthermore, because our institution is a large referral center receiving patients who have failed multiple lines of therapy, our patient population referred for genomic testing and consideration for GMT might be different from the overall population with respect to race, ethnicity, and the number of previous lines of therapy. Moreover, we adopted different criteria to select GMT and non-GMT lines of treatment. Any patient who received GMT treatment after institutional genomic testing was included in the GMT group. However, for the non-GMT group, we selected the first treatment initiated after genomic testing as the non-GMT of interest. This methodology may underestimate the benefit given by GMT. Nevertheless, the median number of previous treatments received in the three genomic cohorts was low, indicating that the patients were generally NGS-tested early and, more importantly, were treated early with targeted treatments during their advanced disease history.

The heterogeneity in our cohorts in part can have contributed to the lack of statistically significant improvement of PFS on multivariable analysis, as well as of on OS analysis. On the other hand, the heterogeneity of our cohorts of patients represents also a strength in the context of a real-world study. In fact, our patients received a variety of GMTs, some of them even in early-phase development within clinical trials, but the improvement in outcomes remains evident. This suggests that a genomic alteration with high actionability evidence should be targeted whenever possible, and, in the context of difficult access to FDA-approved drugs, other ways such as genomically matched clinical trials should be pursued.

In summary, BRAF V600E, TMB-H, and *RET* fusion were found in a wide variety of advanced cancers with clinically meaningful rates. GMT was associated with higher ORR and longer PFS than non-GMT. This article demonstrates that real-world studies in precision medicine can indeed validate clinical benefit observed with agents approved through single-arm genomically selected studies.

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