



# Prospective Genomic Profiling Study in Sarcoma Patients

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## Abstract

**Introduction** Sarcoma is a heterogenous group of malignancy with diverse pathology and clinical behavior. Survival rates differ among histological subtypes, but overall prognosis remains poor due to the scarcity of effective systemic therapies. An insight into the genomic characteristics of different sarcoma histological subtypes enhances our understanding of the disease and highlights potential targeted therapies.

**Objective** We aim to enhance our understanding on the genomic profile of sarcomas and identify actionable genetic variants with the associated targeted therapies.

**Materials and Methods** A prospective tumor genomic profiling study was conducted via next-generation sequencing, involving 30 patients with a diagnosis of soft tissue or bone sarcoma at the University of Malaya Medical Centre. We evaluated the frequency and types of genomic aberrations and identified genomic variants with a therapeutic target.

**Results** A total of 70 genetic mutations were identified. The most frequently involved genes were *TP53* (30.0%), followed by *RB1* (20.0%), *PIK3CA* (10.0%), *KIT* (10.0%), *PDGFR-α* (10.0%), *CKS1B* (10.0%), *KDR* (10.0%), and *MCL1* (10.0%). Genomic alteration involving the *ALK* gene was the only actionable variant identified. The *DCTN1-ALK* fusion was found to be targetable using entrectinib.

**Conclusion** Although the number of actionable variants identified was limited, such data are crucial for the selection of patients into clinical trials on novel therapies in the future and for establishing prognostic biomarkers.

## Keywords

- sarcoma
- genomics
- mutation
- entrectinib

## Introduction

Sarcoma is a rare group of mesenchymal neoplasm, comprising approximately 1% of all adult malignancies.<sup>1</sup> It comprises more than 70 histological subtypes and is especially challenging to study and treat given its diverse pathologies and clinical

trajectories.<sup>2</sup> Survival rates vary across histological subtypes, but overall, prognosis is poor due to the limited effective systemic therapies. Five-year survival rates for metastatic soft tissue and bone sarcoma range between 15 and 24%.<sup>3,4</sup>

An insight into the genomic profile of different sarcoma histological subtypes facilitates our understanding of the

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disease and the potential targeted therapies that may improve prognosis. A high unmet need exists to explore options beyond conventional chemotherapeutic approach in the treatment of inoperable or metastatic sarcoma across different histological subtypes.

In this study, we sought to utilize next-generation sequencing to ascertain the types and prevalence of genetic mutations across various histological subtypes of sarcoma. Our primary goal was to present an in-depth evaluation of the genomic profiles found in sarcoma that could be used to identify therapeutically actionable mutations and their associated targeted therapies. Our hypothesis is that there is a small number of actionable mutations with approved targeted therapies.

## Materials and Methods

### Study Design

This single-center prospective study was conducted from August 2020 to July 2021 at the University of Malaya Medical Centre, a tertiary referral hospital with oncology services in Malaysia. Data cutoff was on July 31, 2021. All participants provided written informed consent prior to any study procedures.

### Patients

Patients with a diagnosis of sarcoma confirmed via histopathological examination and tumor material suitable for genomic assay were deemed eligible for this study. Written informed consent prior to participation was a requirement. For patients under the age of 18 years, a legally authorized representative was required to consent on the patient's behalf. Patients were excluded from the study if they were pregnant or unwilling to provide written informed consent.

The study did not require the patient to attend additional visits to the clinic other than the routine visits planned by their treating doctors during the study inclusion period.

### Sampling Protocol

Patient data including demographics and clinical information were extracted from electronic medical records. Formalin-fixed paraffin-embedded (FFPE) tissue was obtained from each patient. Tumor samples from these patients were either FFPE blocks or 10 to 15 unstained slides with one original hematoxylin and eosin slide. The submission criteria for the submitted tissue samples included at least 25 mm<sup>2</sup> of surface area, and a thickness of 4 to 5 µm. To maintain sensitivity for the detection of genomic alteration, it was a requirement for viable tumor cells to comprise at least 20% of the specimen.

Tumor samples were sent for comprehensive genomic profiling (FoundationOne Heme test) at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (Foundation Medicine, Cambridge, Massachusetts, United States). The FoundationOne Heme test is designed to detect genomic changes across numerous cancer-related genes in sarcomas. DNA sequencing was utilized to interrogate 406 genes and introns of 31 genes, and RNA sequencing for

additional 265 genes. Microsatellite stability was evaluated by analyzing insertion and deletion characteristics at 114 homopolymer repeat loci within or near the targeted gene regions. Tumor mutational burden was established by measuring the number of somatic mutations in the sequenced genes.

The primary outcomes in this study are the prevalence and types of genomic alterations in sarcoma patients. The secondary outcomes are the demographics and the histologic subtypes of sarcoma in our study population.

### Statistical Analysis

Statistical analyses included counts and percentages for categorical variables and the median, minimum, and maximum for continuous variables.

### Ethical Approval

Study approval was granted by the Medical Research Ethics Committee at the University of Malaya Medical Centre on August 11, 2020 (ethics approval number: 2020723- 8909). This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1964) and the International Council on Harmonization guidelines for Good Clinical Practice.

## Results

### Patient Characteristics

Thirty-five patients with histopathological confirmation of sarcoma diagnosis consented to be enrolled in the study. Five patients were excluded as their tumor samples did not meet the quality control standards of the laboratory or our histopathologist (2 insufficient tissue samples, 1 insufficient tissue cellularity, 1 extensive decalcification, and 1 with multiple DNA signatures). Thirty patients underwent tumor genomic profiling.

The baseline characteristics of the 30 sarcoma patients who underwent tumor genetic profiling are summarized in ► **Table 1**. The median age of the patients was 42.5 years, ranging from 21 to 77 years. The majority of the patients were females (66.7%) and Chinese (83.3%). Soft tissue sarcoma was the most common type of sarcoma observed in patients enrolled in this study ( $n=26$ ; 86.7%). Seventeen sarcoma subtypes were identified in total. The most common sarcoma subtype was leiomyosarcoma ( $n=5$ ; 16.7%; ► **Fig. 1**), followed by sarcoma, not otherwise specified ( $n=4$ ; 13.3%). Over 60% of patients had metastatic disease upon participation ( $n=19$ ). Twenty-five patients (83.3%) underwent tumor genomic interrogation via both DNA and RNA sequencing, while five patients (16.7%) had DNA sequencing done only as RNA sequencing failed due to the sample quality.

### Genomic Profile

All patients in this study harbored at least one genetic mutation. The number of genetic mutations found in each patient ranged from 1 to 12, with an average of 3.5. The majority of patients had three or more coexisting genetic mutations ( $n=16$ ; 53.3%). The frequency, distribution and

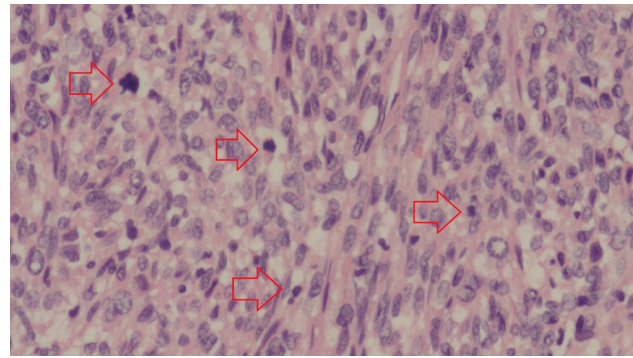
**Table 1** Baseline characteristics of sarcoma patients (n = 30)

Characteristics	Estimates <sup>a</sup>
Age (y)	42.5 (21–77)
<b>Sex</b>	
Male	10 (33.3)
Female	20 (66.7)
<b>Ethnicity</b>	
Malay	3 (10.0)
Chinese	25 (83.3)
Indian	2 (6.7)
<b>Sarcoma types</b>	
Soft tissue	26 (86.7)
Bone	4 (13.3)
<b>Histologic subtypes</b>	
Leiomyosarcoma	5 (16.7)
Sarcoma (NOS)	4 (13.3)
Epithelioid sarcoma	3 (10.0)
Angiosarcoma	2 (6.7)
Liposarcoma	2 (6.7)
Fibrosarcoma	2 (6.7)
Osteosarcoma	2 (6.7)
Rhabdomyosarcoma	1 (3.3)
Ewing's Sarcoma	1 (3.3)
Synovial sarcoma	1 (3.3)
Carcinosarcoma	1 (3.3)
Chondrosarcoma	1 (3.3)
Clear cell sarcoma	1 (3.3)
Myxofibrosarcoma	1 (3.3)
Chordoma	1 (3.3)
Malignant peripheral nerve sheath tumor	1 (3.3)
Solitary fibrous tumor	1 (3.3)
<b>Metastatic disease</b>	
Yes	19 (63.3)
No	11 (36.7)
<b>Genome sequencing</b>	
DNA and RNA analyses	25 (83.3%)
DNA only analysis	5 (16.7%)

Abbreviation: NOS, not otherwise specified.

<sup>a</sup>Estimates are reported as median (range) for age and *N* (%) for categorical variables.

type of genomic aberrations are illustrated in ►Fig. 2 and ►Table 2. A total of 70 genes were found to harbor mutations. The most frequently involved gene was *TP53* (30.0%), followed by *RB1* (20.0%), *PIK3CA* (10.0%), *KIT* (10.0%), *PDGFRA* (10.0%), *CKS1B* (10.0%), *KDR* (10.0%), and *MCL1* (10.0%). Genomic alteration involving the *ALK* gene was the only targetable mutation identified. The *DCTN1*–*ALK*



**Fig. 1** Leiomyosarcoma showing cellular tumor composed of spindle cells that are haphazardly arranged. The nuclei show varying degrees of pleomorphism, and numerous mitotic figures (red arrows) are present (hematoxylin and eosin stain; original magnification ×20 objective).

fusion was found to be targetable using entrectinib in this study.

As illustrated in ►Fig. 3, various types of genomic aberrations were identified in this study. Single nucleotide variants constituted the majority of the variation found (43.1%), followed by amplification (19.6%).

Microsatellite status could not be determined in 2 patients, while the other 28 patients had microsatellite-stable tumors. Tumor mutational burden ranged from 0 to 7 mutations per megabase with an average of 3.0.

## Discussion

In our single-institution cohort, only one actionable mutation was found. It was an *ALK* fusion in a patient with metastatic leiomyosarcoma, which is targetable with entrectinib. Our findings echo that of other large-scale studies that have demonstrated a small number of actionable variants with an approved clinical therapy.<sup>5,6</sup> Of note, we found that patients with fusion-driven sarcomas had no co-occurring mutations, which correlates with findings from the Stanford Cancer Institute cohort.<sup>6</sup>

*ALK* fusions have been identified in soft tissue inflammatory myofibroblast tumors and leiomyosarcoma cases.<sup>7,8</sup> *ALK* fusions that alter the expression of the *ALK* kinase domain have been characterized as oncogenic.<sup>9</sup> In a murine model of leiomyosarcoma with a *KANK2*–*ALK* fusion, monotherapy with lorlatinib, an *ALK* kinase inhibitor, was found to hinder tumor growth and significantly prolong overall survival ( $p < 0.001$ ), providing the first functional validation of an actionable oncogenic kinase fusion in leiomyosarcoma.<sup>8</sup> In our study, entrectinib was found to be a suitable target for our patient who harbored *ALK* alteration in the form of a *DCTN1*–*ALK* fusion. This suggests that distinct *ALK* fusions are targetable by specific *ALK* kinase inhibitors, hence the need for meticulous evaluation of genomic alterations.

Entrectinib is an inhibitor of the tyrosine kinases *TRKA/B/C*, *ROS1*, and *ALK*. Two phase 1 trials (ALKA-372–001 and STARTRK-1) demonstrated that entrectinib was well tolerated with antitumor activity in *NTRK*, *ROS1*, or *ALK* fusion-

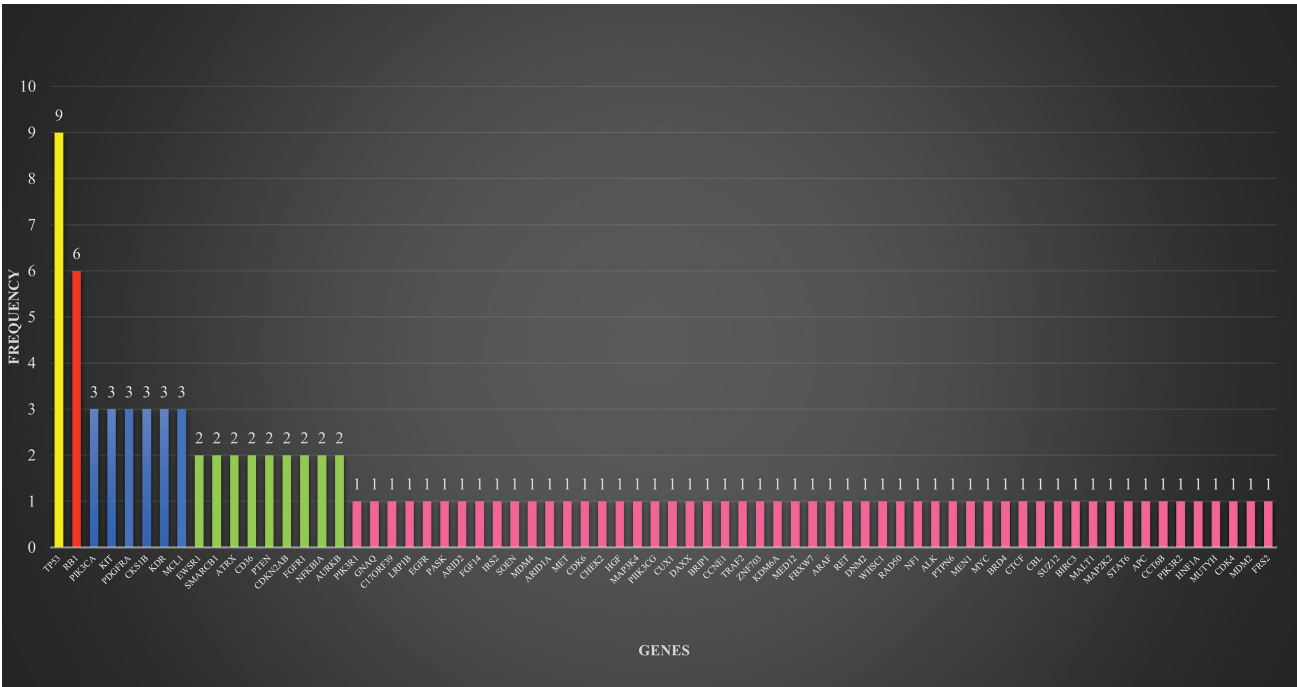


Fig. 2 Frequency and distribution of genomic alterations in sarcoma patients.

Table 2 Types of mutations found for each gene

Genes	Types of mutation
TP53	C229fs*10, L194R, E346fs*24, loss, splice site 994–1G > A, R273C, P152L, H193P
RB1	Loss, R320, L477fs*18, loss exons 1–17, deletion exons 4–17, loss exons 3–27
PIK3CA	V344G, G118D, C378Y
KIT	Amplification
PDGFRA	Amplification
CKS1B	Amplification
KDR	Amplification
MCL1	Amplification
EWSR1	EWSR1-FLI1 fusion, EWSR1-CREB3L1 fusion
SMARCB1	E280, loss
ATRX	Q883fs*13, T1239fs*9
CD36	T111fs*22, Q74
PTEN	Loss exons 1–2, C136R
CDKN2A/B	Loss
FGFR1	N546K, amplification
NFKBIA	R17fs*69, amplification
AURKB	Amplification
PIK3R1	G376R
GNAQ	R183Q
C17orf39	Amplification
LRP1B	R902S
EGFR	P753S

Table 2 (Continued) Types of mutations found for each gene

Genes	Types of mutation
PASK	R1267
ARID2	Rearrangement exon 21
FGF14	Amplification
IRS2	Amplification
SOEN	Rearrangement exon 11
MDM4	Amplification
ARID1A	Q510
MET	Amplification
CDK6	Amplification
CHEK2	Q487
HGF	Amplification
MAP3K4	Rearrangement exon 21
PIK3CG	Amplification
CUX1	Splice site 1516–1G > A
DAXX	Rearrangement exon 2
BRIP1	Rearrangement intron 4
CCNE1	Amplification
TRAF2	Rearrangement exon 2
ZNF703	Amplification
KDM6A	S700fs*29
MED12	G44C
FBXW7	R505C
ARAF	R188H

**Table 2** (Continued) Types of mutations found for each gene

Genes	Types of mutation
RET	R813W
DNM2	Deletion exons 2–11
WHSC1 (MMSET)	E1099K
RAD50	E723fs*5
NF1	S1100
ALK	DCTN1-ALK fusion
PTPN6	R554C
MEN1	R521fs*15
MYC	Amplification
BRD4	Amplification
CTCF	Rearrangement exon 11
CBL	Y371N
SUZ12	Rearrangement intron 4
BIRC3	Loss
MALT1	Amplification
MAP2K2 (MEK2)	Amplification
STAT6	NAB2-STAT6 fusion
APC	C2042fs*2
CCT6B	I4V
PIK3R2	D163fs*24
HNF1A	R131W
MUTYH	Splice site 892-2A > G
CDK4	Amplification
MDM2	Amplification
FRS2	Amplification

positive solid tumors.<sup>10–12</sup> STARTRK-2 trial is a phase 2 basket study of entrectinib in solid tumors. While we await the results of the STARTRK-2 trial to be released, preliminary findings of the trial presented at the 2017 Connective Tissue Oncology Society Annual Meeting have been promising. Three sarcoma patients, two with *ALK* gene fusions and

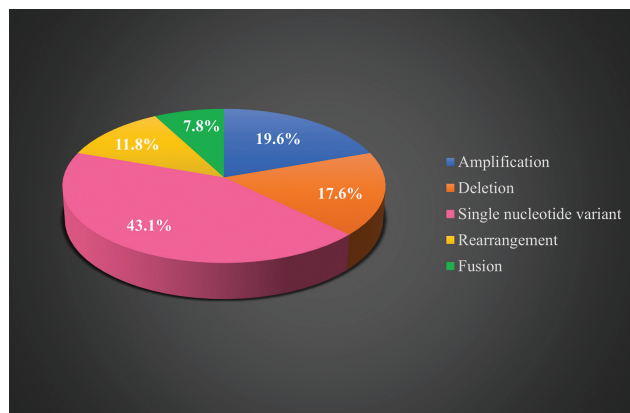
one with *NTRK* gene fusion, have had measurable clinical response to entrectinib.<sup>13</sup> Decrease in tumor size ranged from 30 to 68% by RECIST criteria version 1.1.<sup>13,14</sup>

In our study, *TP53* and *RB1* were among the most frequently mutated genes, at the rates of 30 and 20%, respectively. This corresponds to findings from other large-scale genomic studies on sarcoma patients.<sup>5,6</sup> Functional loss of the tumor suppressor p53 protein, encoded by the *TP53* gene, plays a critical role in tumorigenesis. *TP53* gene mutations have been reported in chondrosarcomas, leiomyosarcomas, and undifferentiated pleomorphic sarcoma.<sup>15,16</sup> Although there are no approved therapies thus far to treat sarcomas with *TP53* alterations, it is worth noting that a small, retrospective study reported improved survival in advanced soft tissue sarcoma patients with *TP53* mutations who were treated with vascular endothelial growth factor (VEGF) inhibitors (18 patients on pazopanib, 1 patient on sunitinib).<sup>17</sup> The authors reported that the progression-free survival (PFS) of patients with *TP53* mutations was significantly greater than *TP53* wild-type tumors (208 vs. 136 days;  $p = 0.036$ ; hazard ratio [HR]: 0.38; 95% confidence interval: 0.09–0.83), when treated with VEGF inhibitors.<sup>17</sup> Larger prospective studies are needed to confirm if *TP53* mutation may serve as a biomarker that predicts response to VEGF inhibitors.

*RB1* encodes the retinoblastoma protein (Rb), a tumor suppressor and cell cycle regulator.<sup>18</sup> Germline mutations in *RB1* account for 40% of retinoblastoma cases and are associated with soft tissue and bone sarcoma, malignant melanoma, and brain tumors.<sup>19,20</sup> There are no approved targeted therapies thus far for *RB1*-mutated sarcomas, and data on its prognostic implications are scarce. Given that *RB1* mutation is highly prevalent in sarcoma and is associated with other types of malignancies, this should prompt the clinician to perform *RB1* germline testing in the appropriate clinical context.

The frequency of *PDGFR-α* and *KIT* mutations in this study was 10%. *PDGFR-α* encodes platelet-derived growth factor receptor  $\alpha$ , a tyrosine kinase receptor that, upon binding of *PDGF-α* or *PDGF-β* ligands, activates several signaling pathways, including *PI3K* and *MAPK*.<sup>21</sup> *PDGFR-α*-mutated gastrointestinal stromal tumors (GISTs) generally have an indolent disease trajectory and are associated with localized disease and a low risk of recurrence.<sup>22</sup> Of note, imatinib has been reported to have limited efficacy specifically in *PDGFR-α* D842V mutated GIST, while other types of *PDGFR-α* mutations appear to be sensitive to imatinib.<sup>22</sup> To date, avapritinib, a selective, potent inhibitor of *KIT*- and *PDGFR-α* mutant kinases, is approved in the United States and the European Union for the treatment of *PDGFR-α* D842V mutated GISTs.<sup>23,24</sup> These approvals were based on findings of the NAVIGATOR trial demonstrating the manageable safety profile and antitumor activity of avapritinib (88% of 56 patients had an overall response, with 5 [9%] complete responses and 44 [79%] partial responses).<sup>25</sup>

*KIT* encodes a cell surface tyrosine kinase receptor that activates the *PI3K*–*AKT* and *RAS*–*MAPK* signaling pathways upon ligand binding and dimerization. Up to 80% of GISTs harbor *KIT* mutations, a targetable genomic alteration

**Fig. 3** Types of genomic aberrations in sarcoma patients.



sensitive to imatinib.<sup>26</sup> *KIT* mutations have also been reported in osteosarcoma and are associated with disease recurrence and shorter survival time.<sup>27,28</sup> Tyrosine kinase inhibitors such as sorafenib and sunitinib have been shown to have clinical benefit in patients with *KIT*-mutated tumors, albeit current evidence is limited to advanced melanoma cases.<sup>29,30</sup>

In this study, *PIK3CA* mutations were reported in 10% of our patients. Although this genomic alteration is still of unknown clinical importance in the treatment of sarcoma, there are clinical data indicating response to therapies targeting *PI3K* (alpelisib) and *AKT* (capivasertib) in *PIK3CA*-mutated breast cancer.<sup>31,32</sup> *PIK3CA* mutations in soft tissue sarcoma have been associated with shorter disease-specific survival.<sup>33</sup> Further studies are needed for characterizing the functional importance of *PIK3CA* mutations in sarcoma and therapies with clinical benefit.

Many patients in our cohort had microsatellite-stable tumors and low tumor mutational burden (mean: 3.0 mutations per megabase). Generally, sarcomas harbor a low median tumor mutational burden of 2.5 mutations per megabase.<sup>34</sup> Reports on microsatellite instability (MSI) in sarcomas in the literature are conflicting and varied due to the diverse methodology for MSI assessment and small sample size in many studies.<sup>35–37</sup> Based on clinical evidence, microsatellite-stable tumors and low tumor mutational burden are associated with reduced sensitivity to immunotherapeutic agents.<sup>38</sup>

Several limitations should be considered when evaluating the clinical significance of our findings. This study is based on a single institution's cohort with a limited sample size. A larger dataset would be beneficial in identifying more actionable variants with the corresponding targeted therapy. It should be noted that five of our patients underwent only DNA analysis instead of DNA and RNA sequencing due to sample quality. Hence, this may have reduced sensitivity for detection of copy number alterations. In addition, genomic alterations that take place throughout one's disease trajectory may not be captured by a single time point biopsy. The possibility of genomic heterogeneity between primary tumor and metastatic sites should be taken into consideration. Utilizing circulating tumor DNA from peripheral blood, which potentially captures DNA from multiple tumor sites, might offer a solution to this issue. This study should prompt future studies using circulating tumor DNA to identify actionable genomic alterations.

## Conclusion

This study shows that sarcomas do carry genetic mutations, some of which are targetable. Although the number of actionable variants identified remains limited, such data will be crucial for the selection of patients into clinical trials on novel therapies in the future and for establishing prognostic biomarkers. An understanding of the type and prevalence of mutations in sarcoma patients may guide treatment decisions and facilitate prognostication.

## Data Availability Statement

The data (i.e., FoundationOne Heme test results) used to support the findings of this study are available from the corresponding author upon request.

## Authors' Contributions

G.F.H. designed, conducted, and supervised the study. E.V.C. conducted the literature search and drafted and edited the manuscript. W.Y.C. performed data collection and assisted the patients in the enrollment process. K.S.M. reviewed and prepared the patients' tumor samples to ensure quality control standards were met for genomic profiling. R.A.M. was involved in patient recruitment. M.S. was involved in patient recruitment.

All the authors reviewed and approved the final manuscript. Each named author has substantially contributed to conducting this study and the writing of this article. This manuscript has been reviewed and approved by all the coauthors.

## Patient's Consent

Written, informed consent was taken from each participant after explanation of the aims, methods, and anticipated benefits of the study.

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## Conflict of Interest

None declared.

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