Original Article

Imatinib in *c-KIT*-mutated metastatic solid tumors: A multicenter trial of Korean Cancer Study Group (UN18-05 Trial)

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ABSTRACT

Introduction: We conducted an open-label, single-arm, multi-center phase II trial to evaluate the efficacy and safety of imatinib chemotherapy-refractory or metastatic solid tumor patients with *c-KIT* mutations and/or amplification.

Methods: *c-KIT* mutations and amplification were detected using NGS. Imatinib (400 mg daily) was administered continuously in 28-day cycles until disease progression, unacceptable adverse events, or death by any cause. The primary endpoint was the objective response rate (ORR).

Result: In total, 18 patients were enrolled on this trial. The most common tumor type was melanoma (n = 15, 83.3%), followed by ovarian cancer, breast cancer, and metastasis of unknown origin (MUO) (each n = 1, 5.5%). The total number of evaluable patients was 17, of which one patient had a complete response, six patients had partial response, and two patients had stable disease. The overall response rate (ORR) of 41.2% (95% CI 17.80–64.60) and a disease control rate of 52.9% (95% CI 29.17–76.63). The median progression-free survival was 2.2 months (95% CI 1.29–3.20), and median overall survival was 9.1 months (95% CI 2.10–16.11). The most common adverse events were edema (31.3%), anorexia (25.0%), nausea (18.8%), and skin rash (18.8%).

Conclusion: Imatinib demonstrated modest anti-tumor activity and a manageable safety profile in chemotherapy-refractory solid tumors with *c-KIT* mutation, especially in melanoma patients.

KEY WORDS: c-KIT mutation, imatinib, melanoma, metastatic solid tumor, NGS

INTRODUCTION

c-KIT is a proto-oncogene on the long arm of chromosome 4 (4q11–4q13) and encodes the SCF receptor (CD117 or KIT).[1,2] KIT is a 145 kDa transmembrane glycoprotein, belonging to class III of the receptor tyrosine kinase (RTK) family. KIT is a type III transmembrane RTK that plays an important role in cancer occurrence.[3] KIT binds to the stem-cell factor (SCF), activating a series of downstream effector pathways involved in fertility, homeostasis, and melanogenesis.[4,5] Deregulation of *c-KIT* could occur in different ways, such as gain of function, loss of function, overexpression, or point mutations to be involved in the process of carcinogenesis.[6] *c-KIT* mutations are observed in various cancers, such as gastrointestinal stromal tumors (GISTs), leukemia, and melanoma. *c-KIT* mutations are observed in approximately 80% of GISTs.[7] Imatinib (formerly STI571; Gleevec in USA and Glivec in Europe; Novartis Pharma, Basel, Switzerland) is a selective inhibitor of BCR-ABL, KIT, and platelet-derived growth factor receptor (PDGFR).[8,9] Imatinib is used successfully in chronic myelogenous leukemia with ABL activation by translocation and overexpression, and GIST.[3,10]

Apart from GIST and melanoma, KIT mutations at low frequencies have been reported in other solid cancers. Molecular profiling of tumors in

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patients referred to a phase I clinical trial at M.D. Anderson Cancer Center showed *c-KIT* mutations in 7 out of a total of 431 patients (2%).[11] Numerous *c-KIT* mutation sites are found in different cancer types, with *c-KIT* mutations occurring within exon 11 in almost 65% of all GIST cases.[7] Most *c-KIT* mutations in melanoma are observed in exon 11 as well with a L576P mutation and an exon 13 mutation.[8,9]

We undertook this study to evaluate the anti-tumor activity of imatinib (Boryung, Korea) in non-GIST solid tumor patients with KIT aberrations in their tumor NGS. Given the low frequency of genomic alteration, we conducted a multi-center trial in Korea where NGS was available in the oncology clinic.

PATIENTS AND METHODS

Study design and treatment

Oral imatinib mesylate (400 mg daily) was administered continuously in 28-day cycles continued treatment until RECIST version 1.1—defined progression, development of unacceptable toxicity, or withdrawal of consent. Baseline assessments consisted of patient history, physical examination, computed tomography (CT) scan or magnetic resonance imaging, and laboratory tests (hematology, coagulation, blood chemistry, and pregnancy test, if indicated). Physical examinations, laboratory tests, and chest X-rays were performed every 4 weeks, and tumor assessment by CT scan was performed every 8 weeks (every two cycles of imatinib) according to RECIST 1.1.[12]

The primary endpoint was the objective response rate (ORR). The secondary endpoints were disease control rate (DCR), progression-free survival (PFS), and safety. All cases of toxicity were identified and examined according to the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) version 4.03. Imatinib was discontinued if patients experienced prespecified treatment-related grade 3 or greater adverse events (AEs). Imatinib re-challenge or dose reduction was allowed at the physicians' discretion after the AEs were resolved. The trial was registered at ClinicalTrials.gov (NCT02461849).

Clinical NGS test

Patients with KIT aberration according to their clinical NGS test at their participating site were available to enter the trial. Briefly, the clinical NGS panels we used were Oncomine cancer panel (Life Technologies, USA), TruSight Oncology 500 (Illumina, USA) assay, or CancerScan (Korea).[13-15]

Patient eligibility

The following was included in the eligibility criteria: patients aged 20 years or older providing complete informed consent prior to any study-specific procedure; patients with metastatic solid tumors with KIT aberration by clinical NGS report; failure to standard of care for cancer treatment. Other eligibility criteria were as following: Eastern Cooperative Oncology Group performance status 2 or lower, at least one measurable lesion based on RECIST v. 1.1, adequate organ function laboratory values—absolute neutrophil count $\geq 1.5 \times 10^9$/L, hemoglobin $\geq$ 9 g/dL, platelets $\geq 100 \times 10^9$/L, bilirubin $\leq 1.5 \times$ upper limit of normal aspartate transaminase/alanine transaminase (AST/ALT) $\leq 2.5 \times$ upper limit of normal [$5.0 \times$ upper limit of normal for subjects with liver metastases], and adequate kidney and heart function. Key exclusion criteria were as following: severe comorbid illness and/or active infections, pregnant or lactating women, history of major surgery or radiotherapy within 4 weeks before study treatment, active CNS metastases not controllable with radiotherapy or corticosteroids, and known history of hypersensitivity to study drugs.

Statistical analysis

The objective response rate (ORR) was defined as the proportion of patients with a complete response (CR) or partial response (PR) to imatinib. DCR was defined as the proportion of patients with CR, PR, or stable disease (SD) in response to treatment. PFS was analyzed using the Kaplan–Meier method from the time of imatinib administration to disease progression, patient request, or any cause of death. All statistical analyses were two-sided, and $P < .05$ was considered statistically significant.

RESULTS

Patient characteristics

Between April 2014 and September 2020, 18 patients with solid tumors and *c-KIT* mutations or amplification detected by NGS, who had failed to standard of care, were enrolled in this study.

Baseline patient characteristics are provided in Table 1. There were eight male patients (44%) and ten female patients (56%). The median age at treatment initiation was 59 years (range, 46–81 years). The most common tumor type was melanoma (n = 15, 83.3%), followed by ovarian cancer (n = 1, 5.5%), breast cancer (n = 1, 5.5%), and MUO (n = 1, 5.5%). Molecular profiling the study population included twelve patients (66.6%) with *c-KIT* mutations, two (11.1%) with *c-KIT* amplification, and four (22.2%) with both aberrations [Table 1]. Patients with both *c-KIT* mutations and amplifications were classified as having mutations (total 16, 88.8%). The most common mutation was L576P, present in six patients (33.3%), and different mutations were observed in each patient.

Efficacy

Among the 18 enrolled patients, one patient was excluded from the final analysis due to withdrawal of patient consent. Among the 17 evaluated patients, one patient with melanoma had complete response (CR) to imatinib, six patients had partial response (PR), and two patients had stable disease with an ORR of 41.2% (95% CI 17.80–64.60) and a disease control rate of 52.9% (95% CI 29.17–76.63) [Figure 1]. The waterfall and

Table 1: Characteristics of the study population

Pt.no	Sex	Age, y	Tumor type	PS	KIT mutation	KIT Amp.	Imatinib Line	Metastasis site	NGS result	Best response
Pt-01	M	62	Acral melanoma	1	KIT L576P	absent	2nd	Lung	CDKN2A deletion	PR
Pt-02	F	63	Acral melanoma	1	KIT L576P	absent	2nd	Distant LN	CDKN2A deletion	PD
Pt-03	M	61	Acral melanoma	1	KIT L576P	absent	5th	Liver, bone, brain	Not found	PR
Pt-04	F	58	Acral melanoma	1	KIT L576P	absent	3rd	Lung	MET amp CDKN2A deletion EGFR amp PDGFRA amp CDK6 amp	PR
Pt-05	F	81	Acral melanoma	1	KIT L576P	absent	4th	Distant LN	BRCA2 deletion NF2 deletion	SD
Pt-06	M	52	Acral melanoma	1	KIT L576P	absent	3rd	Lung	-	PR
Pt-07	F	46	Breast	1	KIT T304A	absent	2nd	Skin	ERBB2 amp CCND1 amp ABCC3 amp	SD
Pt-08	M	71	Acral melanoma	1	KIT N655K	absent	4th	Distant LN	CDK4 amp MDM2 amp	PR
Pt-09	M	63	Cutaneous melanoma	2	KIT D579del	absent	3rd	Distant LN, spine, liver	Not found	PD
Pt-10	F	64	Ovary	1	KIT M537L	absent	3rd	Peritoneum	-	PD
Pt-11	F	77	Acral melanoma	1	KIT I571V	absent	2nd	Pleural seeding	-	Withdrawal
Pt-12	F	47	Mucosal melanoma	1	KITV560A	absent	3rd	Distant LN, lung	Not found	PD
Pt-13	F	70	Mucosal melanoma	1	KIT W557G	present	3rd	Liver, spleen	PDGFRA amp	PR
Pt-14	M	56	Acral melanoma	1	KIT K642E	present	6th	Lung	PDGFRA amp	CR
Pt-15	M	56	Cutaneous melanoma	1	KIT K642I	present	4th	Distant LN, liver	-	PD
Pt-16	F	53	MUO	1	absent	present	4th	Cervical, retroperitoneum, distant LN	-	PD
Pt-17	F	56	Mucosal melanoma	1	KIT N882Y	present	2nd	Lung, liver	-	PD
Pt-18	M	54	Acral melanoma	1	absent	present	6th	Lung, Pleura seeding	-	PD

swimmer plot of evaluable patients are provided in Figure 1. Pt-14 with KIT K642E mutation had achieved CR for >1 year. Pt-04 and pt-06 melanoma patients with KIT L576P mutation showed prolonged PR to imatinib. Both patients had lung metastases and failed to prior pembrolizumab treatment. All melanoma patients (N = 15) enrolled on this trial failed to pembrolizumab or nivolumab as prior treatment. Pt-03 with L576P mutated melanoma has failed to four lines of treatment including anti-PD1 antibody. The patient had metastases to liver, bone, brain, but has achieved PR to imatinib for >30 weeks at the time of this writing. Pt-13 melanoma patient with KIT W557G mutation received imatinib as third line and achieved PR. Taken together, metastatic melanoma patients who have failed to anti-PD-1 treatment demonstrated durable response to imatinib. These patients had KIT K642E, L576P, or W557G, N655K mutations which are known activating mutations. Next, we analyzed the genome landscape with available clinical NGS data [Figure 2]. Of note, patients with PR had concurrent genomic aberrations besides KIT, such as ATM, NF1, and TP53. Interestingly, although limited from small sample size, patients seem to respond to imatinib regardless to concurrent genomic aberration if they have strong activating mutations such as K642E, L576P, or W557G, N655K. In our series, we did not find significant difference in response according to concurrent KIT amplification with KIT mutations. Nevertheless, patients with KIT amplification without activating KIT mutations did not respond to imatinib (Pt-16, Pt-18). Hence, activating KIT mutation was important to predict response to imatinib regardless to concurrent passenger mutations [Figure 2]. In lollipop diagram, we analyzed maximal tumor shrinkage with each KIT genomic aberration [Figure 3a]. In this figure, we could clearly observe that patients with maximal tumor shrinkage were the ones with KIT W557G, N655K, and L576P. In addition, patients with KIT amplification only did not experience tumor shrinkage. Representative CT results for Pt-13 are shown in Figure 3b. This patient was a 70-year-old female with multiple liver metastases. The patient has failed to prior anti-PD1 treatment and dacarbazine-based treatment. The patient had multiple liver and spleen metastases. Eight weeks after imatinib treatment, the patient achieved PR [Figure 3b].

The median PFS was 2.2 months (95% confidence interval [CI] 1.29–3.20). The median overall survival was 9.1 months (95% CI 2.10–16.11) [Figure 4]. There was no significant difference in OS according to *c-KIT* gene status (mutated or amplified).

Safety

The safety profile of the study population is provided in Table 2. The most frequently observed AEs were edema (29.4%), anorexia (23.5%), nausea (17.6%), skin rash (17.6%), fatigue (11.8%), myalgia (11.8%), and pneumonia (11.8%). Grade 3 or more AEs were observed in two patients, with

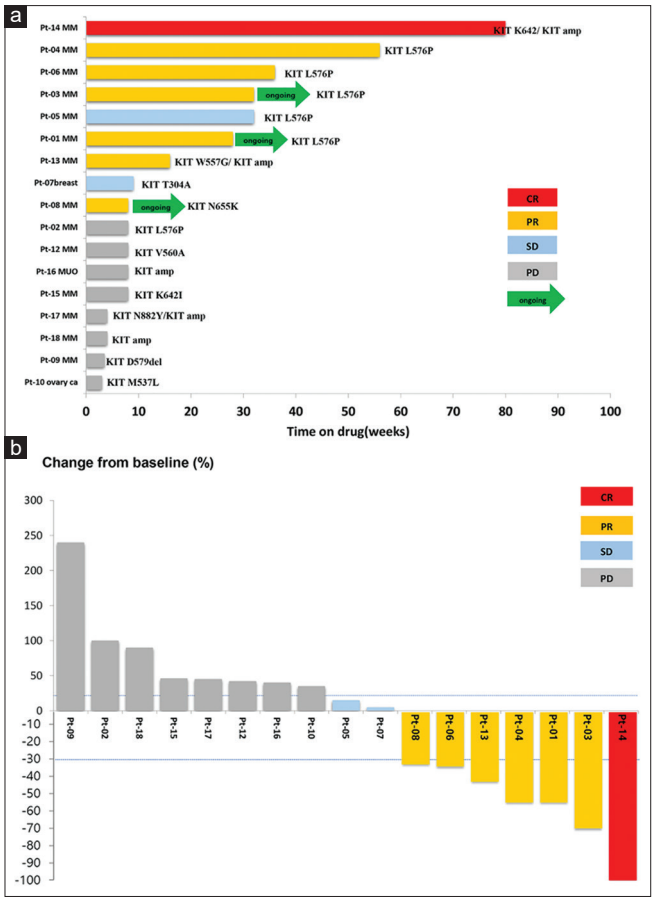

Figure 1: (a) Swimmer plot of treatment duration for 17 evaluable patients. (b) Waterfall plot for 13 evaluable patients. The y-axis indicates the percentage of maximum tumor reduction assessed according to RECIST.1.1 criteria. *MM* malignant melanoma; *MUO* metastasis of unknown origin; *CR* complete response, *PR* partial response; *SD* stable disease; *PD* progressive disease; *RECIST* Response Evaluation Criteria in Solid Tumors

Table 2: Treatment-related adverse events

Adverse events	All grades	%	Grade ≥3	%
Edema	5	29.4		
Anorexia	4	23.5		
Nausea	3	17.6		
Skin rash	3	17.6	1	5.9
Fatigue	2	11.8		
Myalgia	2	11.8		
Pneumonia	2	11.8		
Alopecia	1	5.9		
Anemia	1	5.9	1	5.9
Constipation	1	5.9		
General weakness	1	5.9		
Neutropenia	1	5.9		
Sensory neuropathy	1	5.9		

one patient having grade 3 skin rash (5.9%) and one having grade 3 anemia (5.9%). Four patients required an imatinib dose reduction (two patients with edema, and one patient each with skin rash and weakness, respectively). None of the patients discontinued treatment due to AEs, and there were no treatment-related deaths.

DISCUSSION

The present prospective study demonstrates the efficacy and safety of imatinib in chemotherapy refractory, metastatic solid tumors from a multicenter phase II study in patients with *c-KIT* mutation and/or amplification. CR was achieved in one patient, PR in two patients, and SD in two patients who received imatinib, with an ORR of 41.2% and a DCR of 52.9%. The median PFS was 2.2 months, and the median overall survival was 9.1 months. In addition, imatinib demonstrated a well-tolerated safety profile in solid cancer patients.

As described earlier, except for GIST and melanoma, other solid cancers are reported to have low frequencies of *c-KIT* mutations. For instance, *c-KIT* mutations are uncommon in AML and are present in only 26% of germ cell cancers, and more specifically, testicular seminomas, have been associated with *c-KIT* mutations.[7,16,17] KIT expression was confirmed through immunohistochemistry (IHC) in 64% small-cell lung cancer patients; however, no *c-KIT* exon 11 mutations were detected.[18] Similarly, of the 53 adenocystic carcinomas investigated in two studies, none had *c-KIT* exon 11 and 17 mutations, despite increased KIT expression using IHC.[7,19,20] Sihto *et al*. conducted *c-KIT* mutation analysis in 334 cancer patients, and only 15 *c-KIT* mutations were found; however, all 15 patients had GIST, and no *c-KIT* mutations were found in other cancers.[11,19]

Despite the low incidence of *c-KIT* mutations in solid cancers, with relatively higher *c-KIT* mutations in GIST and melanoma, the use of imatinib improved prognosis. Previously completed phase II studies on imatinib in unselected patients with melanoma failed to demonstrate clinical activity.[21,22] However, use of imatinib in patients with metastatic melanoma harboring *c-KIT* mutations or amplification improved PFS and OS.[8,23] Various *c-KIT* mutation sites have been discovered according to cancer type. *c-KIT* mutations occur within exon 11 in almost 65% of all GIST cases.[7] Most *c-KIT* mutations in melanoma are observed in exon 11 (similar to GIST) with L576P mutation,[8,23] as also observed in our study in 6 out of 15 melanoma patients (40%). In various studies, dramatic responses in patients with melanomas harboring this mutation were observed.[16,24] In our study, 5 out of 6 melanomas with the *c-KIT* L576P mutation showed more SD in the response evaluation. *c-KIT* K642E and N655K mutations also showed partial response. A prior study in GIST showed sensitivity in patients with K642E and N822K *c-KIT* mutations and the resistance in patients with V654A and D820Y *c-KIT* mutations to imatinib.[25] All melanoma patients who were enrolled onto this study were refractory to pembrolizumab or nivolumab prior to enrollment. In line with our previous study, melanoma patients with both *c-KIT* mutations or amplification were less sensitive to imatinib.[26]

c-KIT mutations are uncommon in most malignant solid tumors, and such mutations may exist within a single histological cancer type. Clinical NGS was used

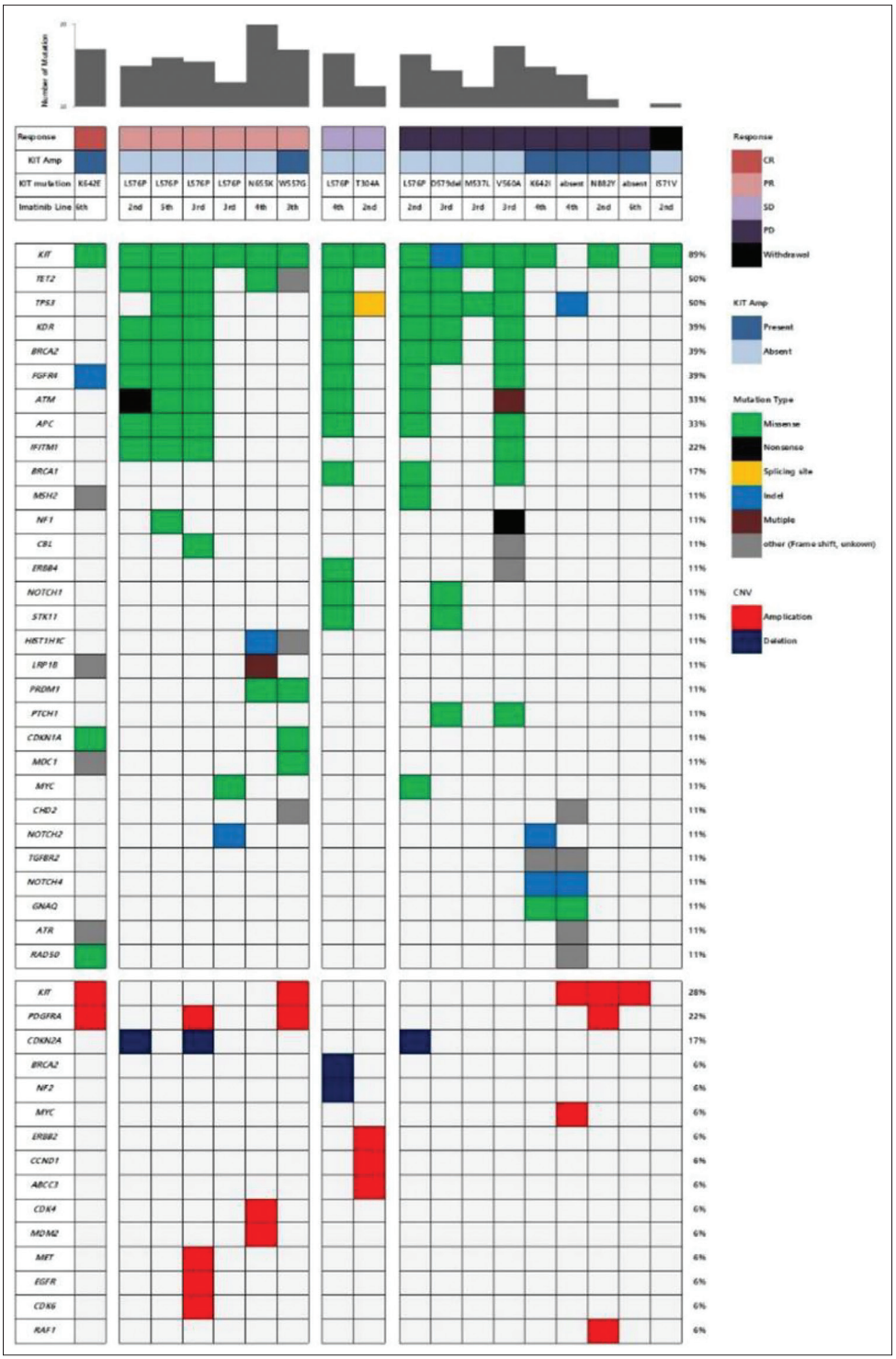

Figure 2: Genomic landscape of clinical and molecular features for all patients

to guide therapy in thymic carcinoma, which is a rare treatment-refractory solid malignancy, and several different *c-KIT* mutations have been associated with its sensitivity to TKIs.[27] *c-KIT* is involved in several signaling pathways in cancer cells, such as the Ras-Erk pathway, PI3K/AKT pathway, and Src-signaling pathway. Although each signaling pathway is different and has different effects on cell function, the result of all three pathways is the inhibition of cell apoptosis, resulting in oncogenesis through cell proliferation, growth progression, or migration.[28,29]

Over the past decade, rapid developments in the efficacy of melanoma therapeutics have been made. Clinical therapeutics for metastatic melanoma have improved dramatically with the development of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell-death protein 1 (PD-1)

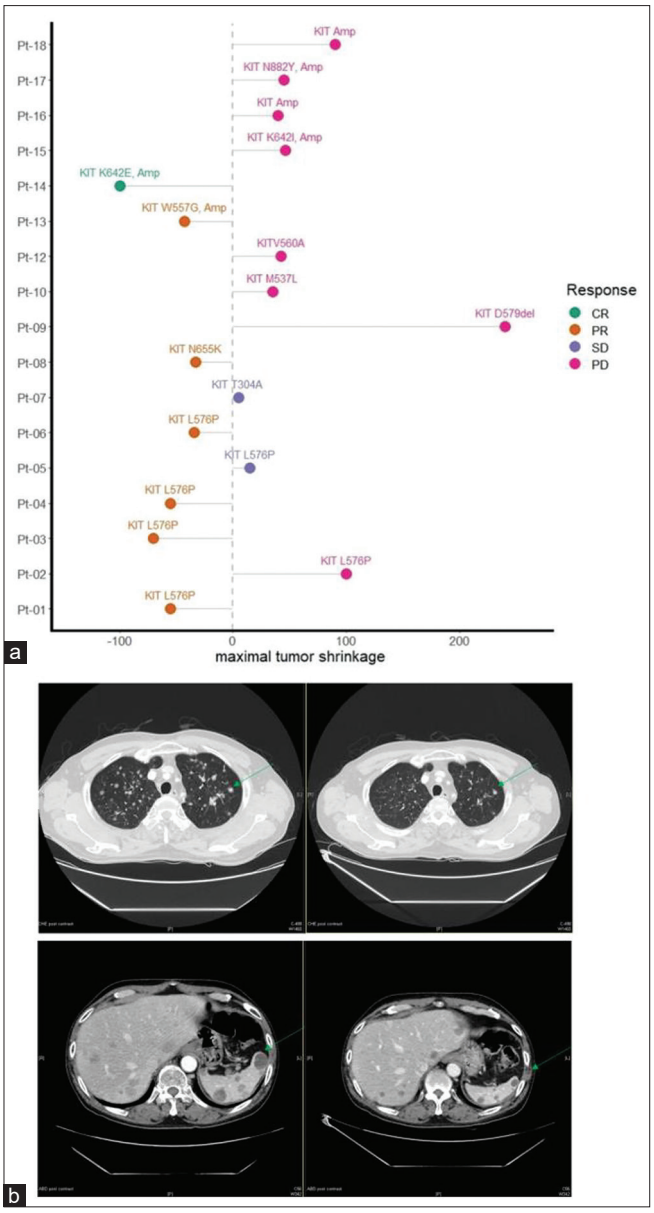

Figure 3: (a) Lollipop diagram of molecular alterations and drug efficacy for each patient. Demonstration of each patient's KIT mutation/amplification and the maximal tumor size with imatinib. (b) Representative computed tomography results were shown for the patient 13, who was a 70-year woman with a primary melanoma with multiple liver metastasis. W557G mutation was detected in exon 11 of the c-Kit gene. Eight weeks after the first treatment, the response was evaluated by CT

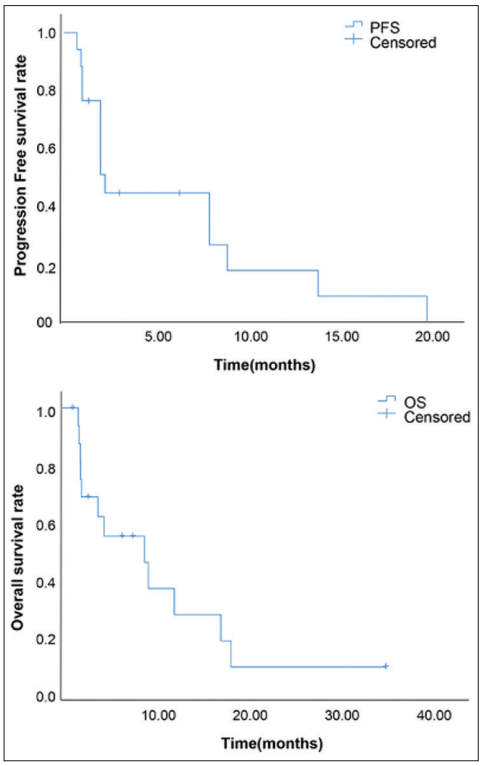

Figure 4: Kaplan–Meier curves. PFS for imatinib treatment in eligible patients with chemotherapy-refractory solid tumor harboring KIT mutation/amplifications. OS for imatinib treatment in eligible patients with chemotherapy-refractory solid tumor

blocking antibodies, and BRAF and MEK inhibitors associated with improved overall survival.[30] Although these treatments are not as effective, imatinib may be a treatment option for refractory melanoma with *c-KIT* mutations, especially those with L576P mutation. Taken together, imatinib showed modest anti-tumor efficacy and a well-tolerated safety profile in patients with chemotherapy-refractory or metastatic solid cancer and *c-KIT* mutations, especially in melanoma patients. Imatinib can be a feasible treatment option for melanoma patients who failed to previous treatment including anti-PD1 therapy.

Ethical approval statement

All patients provided written informed consent before enrollment in accordance with the Declaration of Helsinki, and the Institutional Review Board of Samsung Medical Center approved all study procedures.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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