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Original Research

A phase II study on the efficacy of regorafenib in treating patients with c-*KIT*-mutated metastatic malignant melanoma that progressed after previous treatment (KCSG-UN-14-13)

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Abstract ***Background:*** c-*KIT* mutations are found in approximately 15% of patients with malignant melanoma in the Asian population. Regorafenib, an oral multikinase inhibitor, acts against both wild-type and mutant KIT.
Objective: This multi-institutional, phase II, single-arm study aimed to evaluate the efficacy of regorafenib against metastatic malignant melanoma harbouring c-*KIT* mutations.

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Methods: Patients with metastatic melanoma positive for c-*KIT* mutations, upon progression after at least one line of systemic treatment, were enroled. Patients received oral regorafenib 160 mg once daily for 3 weeks (4-week cycle). The primary endpoint was disease control rate (DCR), and secondary endpoints were safety, overall response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: In total, 23 patients were enrolled. c-*KIT* mutations were frequently reported in exon 11 (14/23, 60.9%), followed by exons 13, 17, and 9 in 5 (21.7%), 5 (21.7%), and 2 (8.7%) patients, respectively. DCR at 8 weeks was 73.9%, with 2 patients (8.7%) achieving complete response, 5 (21.7%) achieving partial response, and 10 (43.5%) showing stable disease. ORR was 30.4% (7/23). The median follow-up period was 15.7 months (95% confidence interval [CI], 9.6–21.3), and median OS and PFS were 21.5 months (95% CI, 15.1–27.9) and 7.1 months (95% CI, 5.0–9.2), respectively. Circulating tumour DNA analysis in selected patients showed high c-*KIT* correlation (85.7%) with tissue-based tumour mutational profiles. The most common adverse events (AEs) were skin reactions, including palmar-plantar erythrodysesthesia (52.2%), and grade 3 AEs were reported in 39.1% (9/23) of the patients.

Conclusion: Regorafenib in second- or later-line settings demonstrated significant activity in patients with metastatic melanoma harbouring c-*KIT* mutations.

1. Background

With recent advances in molecular biology, a paradigm shift has occurred in the treatment of malignant melanoma, including targeted therapy with potential therapeutic targets *BRAF, NRAS*, and c-*KIT* [1,2]. While non-chronic sun-damaged (non-CSD) melanomas often harbour oncogenic *BRAF* or *NRAS* mutations, these mutations are less frequent in CSD, acral, or mucosal melanomas. Instead, c-*KIT* mutations are more common in mucosal and acral melanomas, with a higher prevalence of approximately 10–15% in the Asian populations, including South Korea [3–7].

c-*KIT* encodes type III transmembrane receptor tyrosine kinase, and the binding of its ligand, stem cell factor, to the receptor results in receptor dimerization, autophosphorylation, and activation of several signalling pathways pertinent to normal melanocyte development, migration, survival, proliferation, and differentiation [8]. Targeting *KIT* mutations using the small-molecule inhibitor imatinib mesylate has shown significant clinical benefits in gastrointestinal stromal tumors (GIST) [3] as well as in malignant melanoma, where notably, tumours containing c-*KIT* mutations showed a superior response to those harbouring *KIT* amplifications [9,10].

Regorafenib, an oral diphenylurea multikinase inhibitor, demonstrates activity against various kinases including wild-type and mutant KIT, *in vitro* and *in vivo* [11]. It has previously shown promising antineoplastic activity for GIST, hepatocellular, and colorectal cancer patients [12–14]. However, to our knowledge, no previous clinical trial has evaluated the clinical efficacy of regorafenib in treating malignant melanoma.

In this study, we aimed to evaluate the efficacy of regorafenib in patients with metastatic malignant melanoma harbouring the c-*KIT* mutation that had progressed with previous systemic therapy.

2. Methods

2.1. Study overview

This multicentre, single-arm, phase II trial evaluating the efficacy of regorafenib in patients with recurrent/metastatic malignant melanoma harbouring the c-*KIT* mutation was conducted in seven institutions in South Korea. Eligible patients had recurrent/metastatic melanoma with c-*KIT* mutations detected using either polymerase chain reaction or next-generation sequencing (NGS), disease progression after at least one line of systemic treatment, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2, age ≥19 years, measurable or evaluable disease in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [15], and adequate bone marrow, renal, and hepatic functions. Exclusion criteria included uncontrolled brain and central nervous system metastases, prior exposure to KIT inhibitors, presence of *BRAF* mutations, any unresolved toxicity of grade ≥2 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.0) due to prior systemic therapy, and history of concomitant malignancy within 3 years (with the exception of completely resected skin cancer [non-melanoma], in situ carcinoma of the cervix, or previous cancer deemed "no evidence of disease" for > 5 years).

2.2. Treatment and study assessment

Patients received 160 mg of oral regorafenib once daily for 3 weeks in a 4-week cycle. Dose interruptions or reductions of up to two levels (120 and 80 mg) were allowed for clinically relevant adverse events (AEs). Tumour assessment was performed according to RECIST version 1.1 at baseline and after every two cycles of treatment or when clinically indicated.

Patients were treated until radiologic disease progression, occurrence of unacceptable toxicity, or study withdrawal. Efficacy analysis was performed for the intention-to-treat (ITT) population. Safety was assessed in patients who received at least one dose, which included evaluation of vital signs, physical status, ECOG PS, AEs, and laboratory values. All AEs were graded and recorded as per the NCI-CTCAE version 4.0 [16].

After treatment completion, disease progression and survival status were determined for all patients during follow-up visits every 3 months. Data regarding subsequent therapy and patient survival were obtained from telephonic interviews and outpatient clinic records.

2.3. Exploratory analysis

For a subset of patients, additional blood samples were collected for predictive biomarker and circulating tumor DNA (ctDNA) analyses. For targeted panel sequencing, a DNA NGS library was first constructed and solution-based target enrichment was performed using the AlphaLiquid® 100 target capture panel, including 118 cancer-related genes (IMBdx, Inc. Seoul, South Korea) [17]. The captured DNA libraries were sequenced using the Illumina NextSeq 550 Dx platform (Illumina). For each patient, a longitudinal analysis of ctDNA was performed at baseline, mid-treatment, and disease progression, if available.

2.4. Statistical analysis

The primary endpoint of the study was disease control rate (DCR) (rate of complete response [CR], partial response [PR], or stable disease [SD] as the best response in accordance with RECIST version 1.1). Secondary endpoints were overall response rate (ORR), defined as the percentage of patients achieving either CR or PR as the best response, progression-free survival (PFS), overall survival (OS), and safety profiles. PFS was defined as the time from initial regorafenib dose until disease progression or death from any cause, whereas OS was defined as the time from initial dose until death from any cause. In case of tracking and observation discontinuation before disease progression or death, treatment discontinuation owing to toxicities, administration of unauthorised chemotherapy, or consent withdrawal by patient, the applicable data were censored at the last observation point. Survival analysis, including PFS and OS, was performed using the Kaplan–Meier method.

The sample size was determined to test the null hypothesis of DCR ≤28% [18] against the alternative hypothesis of DCR ≥50% [9,10] at a 5% significance level. The hypotheses were tested with 80% statistical power and 10% significance level, and 32 patients were required for response assessment. Considering a dropout rate of 10%, the required number of participants was 36.

Statistical analyses were performed using Prism 8 (GraphPad Software, Inc., La Jolla, CA, USA) or SPSS (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp). All tests were two-sided, with a significance level of < 0.05.

3. Results

3.1. Patient characteristics

Between December 2014 and January 2022, 153 patients were screened for c-*KIT* mutations, of which 33 had c-*KIT* mutations. Ultimately, 23 patients who met all criteria were enrolled and started on regorafenib. At the final data cutoff point of November 30, 2022, one patient was receiving ongoing treatment and 22 patients had terminated treatment: 19 (82.6%) owing to disease progression, one (4.3%) owing to toxicity, and two (8.7%) withdrew participation (Supplementary Fig. 1).

The median age at baseline was 68 (range, 31–86) years, and there were 11 males (47.8%) and 12 females (52.2%). The melanoma subtype distribution was as follows: nine (39.1%) acral, six (26.1%) mucosal, and three (13.0%) CSD. The most common mutation site was exon 11 (14 patients, 60.9%), followed by exons 13, 17, and 9 in 5 (21.7%), 5 (21.7%), and 2 (8.7%) patients, respectively. Two patients had c-*KIT* mutations at multiple sites: one patient in exons 9 and 11, and the other patient in exons 9, 13, and 17. Most patients had received one prior line of systemic therapy (17 patients, 73.9%), with five (21.7%) and one (4.3%) patients receiving two and three lines of prior systemic therapy, respectively. A total of 69.6% (16/23) of the patients received immune checkpoint inhibitors (ICIs) including anti-programmed death receptor 1 (anti-PD-1) and anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) prior to study enrolment. Baseline clinical characteristics are shown in Table 1.

3.2. Clinical activity and efficacy of regorafenib in the ITT population

Radiologic responses at 8 weeks were available for 21 of 23 patients. Two patients withdrew consent during the first cycle of treatment before the intended tumour assessment. The median treatment duration was 5.8 months (95% confidence interval [CI], 2.3–10.7). Individual tumour responses and c-*KIT* mutation sites are shown in Table 2.

DCR was 73.9% (17/23 patients, 95% CI, 51.6–89.8%), with two patients (8.7%) showing CR, five (21.7%) showing PR, and 10 (43.5%) showing SD. ORR was 30.4% (7/23 patients, 95% CI, 13.2–52.9%) (Table 3). Tumour shrinkage was observed in 77.8% (14/18) of patients with measurable target lesions; the waterfall plot showing the best tumour shrinkage from the baseline is illustrated in Fig. 1. The median follow-up

Table 1
Patient demographics and baseline characteristics.

N = 23		No. of patients (%)
Median age (range), year		68 (31–86)
Sex	Male	11 (47.8)
	Female	12 (52.2)
Melanoma subtype	CSD	3 (13.0)
	acral	9 (39.1)
	mucosal	6 (26.1)
	unknown	5 (21.7)
Stage at diagnosis	I	3 (13.0)
	II	5 (21.7)
	III	5 (21.7)
	IV	7 (30.4)
	Unknown	3 (13.0)
Disease stage	M1a	8 (34.8)
	M1b	5 (21.7)
	M1c	8 (34.8)
	M1d	2 (8.7)
ECOG status	0	10 (43.5)
	1	13 (56.5)
Baseline LDH	≤ ULN	9 (39.1)
	> ULN	14 (60.9)
C-kit mutation status[a]	exon 9	2 (8.7)
	exon 11	14 (60.9)
	exon 13	5 (21.7)
	exon 17	5 (21.7)
Prior radiotherapy	Yes	14 (60.9)
	No	9 (39.1)
Prior surgery	Yes	20 (87.0)
	No	3 (13.0)
No. of prior systemic therapy	1	17 (73.9)
	2	5 (21.7)
	3	1 (4.3)
Choice of prior systemic therapy[b]	Cytotoxic chemotherapy	11 (47.8)
	Immunotherapy	16 (69.6)
	Interferon	3 (13.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CSD, chronic sun damage; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a] Multiple mutations at different exons were present in two patients.
[b] Choice of prior therapy: one patient had received both prior cytotoxic chemotherapy and immunotherapy.

period was 15.7 months (95% CI, 9.6–21.3), and median OS and PFS were 21.5 (95% CI, 15.1–27.9) and 7.1 months (95% CI, 5.0–9.2), respectively (Fig. 2A, B).

To assess the effect of treatment according to c-*KIT* mutation site, we divided the patients into two groups, as follows: the exon 11 mutation group comprising 14 patients (60.9%) and the non-exon 11 mutation group comprising 9 patients (39.1%). Among these, one patient with mutations in both exons 9 and 11 was included in the exon 11 group, while the non-exon 11 group consisted only of patients harbouring mutations in exons 9, 13, and 17.

ORRs for exon 11 and non-exon 11 mutation groups were 28.6% and 33.3%, respectively, and DCRs were 71.4% and 77.8%, respectively, with no significant difference between the two groups. No significant differences were found between those who had received prior ICI treatment and those who had not, with ORRs of 37.5% and 14.3%, and DCRs of 75.0% and 71.4%, respectively.

Survival analysis showed a discrepancy between the two groups, as the exon 11 mutation group showed significantly worse OS of 18.3 months (95% CI, 14.2–22.4) than did the non-exon 11 mutation group of 24.9 months (95% CI, 15.6–34.2, $P = 0.042$). The exon 11 mutation group tended to have shorter PFS, although not significant, than the non-exon 11 mutation group (5.3 [95% CI, 3.2–7.3] versus 7.1 months [95% CI, 3.6–10.6], $P = 0.766$) (Fig. 2C, D). The survival rates did not significantly differ between the prior ICI exposure and non-exposure groups.

3.3. AEs and tolerability

Skin reactions were the most common adverse event, with palmar-plantar erythrodysesthesia (PPE) in 12 (52.2%) patients, and skin rash other than PPE in 7 (30.4%) patients. All reported PPE were either grade 1 or 2 AEs. Treatment-related grade 3 AEs occurred in nine patients (39.1%, total 10 events), including but not limited to skin rash, infection, aspartate aminotransferase elevation, thrombocytopenia, and neutropenia. No grade 4 toxicities or treatment-related deaths occurred during the study period (Table 4).

AEs were generally manageable according to the standard guidelines and dose modifications. Sixteen patients (69.6%) experienced either dose interruption or reduction, and of these, eight patients (34.8%) underwent dose reductions twice to 80 mg.

3.4. ctDNA analysis results and their correlation with tissue sample analysis results

Serial blood samples were collected from 11 patients at baseline and various time points throughout their treatment duration, including the first response assessment (Table 2, Patients 1–11). Single ctDNA samples at baseline were available for eight patients, and paired samples at baseline and the first response time point were available for three patients.

Sufficient input cell-free DNA (> 20 ng) for NGS was extracted from 1 to 4 mL of plasma collected from the 11 patients. ctDNA was detected in all 11 patients, except for one patient whose ctDNA was not detected at baseline but was detected at the first response evaluation. Allele fractions ranged from 0.08% to 24.35% and mutations with allele frequencies between 40% and 60% were deemed likely to be germline variants.

Seven patients (7/11, 63.6%) harboured c-*KIT* mutations as per the plasma-based ctDNA analysis, and in six out of seven patients (85.7%), *KIT* alteration sites were in concordance with their matching tissue-based analysis results. One patient who did not show a correlation had a c-*KIT* p.K642G substitution in exon 13 in

Table 2
Tumour characteristics and response to regorafenib of each patient.

Patient	Sex	Age	Subtype	c-*KIT* mutation	M stage	Prior Treatment	Months of Treatment	LDH	Best Response	Time to progression	Survival [months]	Survival Status
1	F	58	Unknown	exon 11	M1d	Dacarbazine	4	201	SD	4	7.6	Dead
2	F	72	*Mucosal*	exon 9,13,17	M1c	Ipilimumab	5.8	277	SD	7.1	10.2	Dead
3	M	80	Mucosal	exon 17	M1c	Dacarbazine/Interferon	11.8	318	SD	11.6	24.4	Dead
4	F	75	Acral	exon 13	M1b	Dacarbazine	2.1	187	PD	2.1	16.3	Dead
5	M	76	Acral	exon 11	M1c	Dacarbazine	5.8	249	SD	5.8	21.5	Dead
6	F	31	CSD	exon 11	M1b	Pembrolizumab, Dacarbazine	22.5	93	PR	21.8	22.9	Dead
7	F	66	Mucosal	exon 11	M1d	Pembrolizumab	10.1	216	PR	10.1	12.3	Alive
8	F	69	Mucosal	exon 11	M1c	Pembrolizumab	4.2	219	SD	4	10	Alive
9	F	86	CSD	exon 11	M1c	Interferon, Pembrolizumab	16.9	211	PR	16.8	17.8	Alive
10	F	85	Mucosal	exon 11	M1c	Pembrolizumab	2.1	323	PD	1.8	5	Alive
11	M	62	Acral	exon 13	M1a	Pembrolizumab (adjuvant), Dacarbazine	6	221	SD	5.8	7.6	Alive
12	M	64	Unknown	exon 17	M1c	Pembrolizumab	0.3	134	-	-	21.3	Alive
13	F	68	Unknown	exon 11	M1a	Interferon, Dacarbazine/Interferon	15.7	415	CR	-	15.7	Alive
14	F	61	Acral	exon 17	M1b	Pembrolizumab	11.6	483	PR	11.6	24.9	Alive
15	M	59	Acral	exon 11	M1c	Pembrolizumab	3	413	PR	3.1	18.3	Dead
16	F	81	Mucosal	exon 17	M1a	Pembrolizumab	7.3	408	CR	7.1	30.2	Dead
17	M	67	Acral	exon 11	M1a	Pembrolizumab	2.1	650	PD	2.1	4.2	Dead
18	M	84	Unknown	exon 11	M1a	Pembrolizumab	0.9	340	PD	0.8	4.3	Dead
19	M	47	CSD	exon 13	M1a	Interferon, Pembrolizumab, Dacarbazine	49	441	SD	48.7	48.7	Alive
20	M	60	Acral	exon 13	M1b	Pembrolizumab	9.6	554	PR	9.6	12.6	Alive
21	M	79	Acral	exon 11	M1a	Dacarbazine, Nivolumab	10.7	150	PR	-	16.7	Alive
22	M	68	Acral	exon 11	M1b	Cisplatin/Vinblastin/Dacarbazine	0.2	969	-	-	0.6	Dead
23	F	64	Unknown	exon 9, 11	M1a	Cisplatin/Vinblastin/Dacarbazine	2.3	279	SD	16.1	16.1	Dead

Table 3
Clinical activity of regorafenib.

Response Evaluation	All patients ($N = 23$)	
	No	%
Overall response rate[a]	7	30.4
Complete response	2	8.7
Partial response	5	21.7
Stable disease	10	43.5
Progressive disease	4	17.4
Not evaluated	2	8.7
Disease control rate[b]	17	73.9

[a] Overall response rate includes complete response and partial response.
[b] Disease control rate includes complete response, partial response, and stable disease.

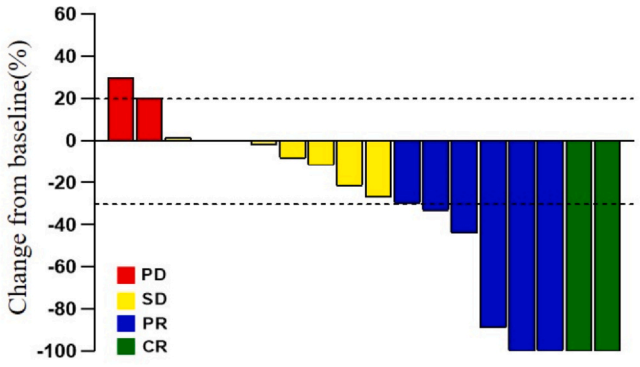

Fig. 1. Waterfall plot of best tumour shrinkage from baseline. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

the original tumour tissue-based analysis; however, plasma c-*KIT* analysis showed a synonymous mutation at p.D820, which is a different site in exon 17. In addition to the tissue-plasma concordant c-*KIT* mutations, ctDNA analysis further detected c-*KIT* amplification (copy number variation 4.5) in one patient and an additional c-*KIT* mutation site previously not detected in tissue analysis (p.D266N) in another patient.

In one patient who achieved PR, including the disappearance of all target lesions, serial plasma samples were obtained at multiple time points: baseline, first response, and disease progression. The tissue-correlated c-*KIT* mutation was first detected at baseline with a variant allele frequency (VAF) of 0.18% but became undetectable at later time points. In another patient, the VAF of c-*KIT* was 0.20% at baseline and 0.11% at the first response, increasing to 0.21% at disease progression. The patient's best tumour response remained stable until disease progression.

4. Discussion

In this multicentre phase II trial, regorafenib showed comparable efficacy to previously reported c-*KIT*-targeting agents nilotinib and imatinib for melanoma (Table 5) [3,9,10,19–22]. The clinical efficacy of regorafenib was also comparable to that of the ICIs nivolumab and pembrolizumab, as second-line therapies, with ORRs of 31.7% and 32.9%, respectively [23,24]. The majority of c-*KIT*-positive patients in this study had acral or mucosal melanoma subtypes, and only 3 of 23 patients (13.0%) had the CSD subtype, which strongly reflects the predilection of malignant melanoma subtypes in the Asian population.

While previous ICI treatment did not affect the efficacy of regorafenib in terms of survival outcome, in the future, approaches involving regorafenib use may necessitate combination with immunotherapy agents, as ICI is currently routinely used as the mainstay of treatment. In a recent phase II study by Si et al., imatinib in combination with anti-PD-1 antibody toripalimab showed an ORR of 58.8% and DCR of 82.4%, with notably higher response rates for patients harbouring exon 11 mutations [25].

To determine whether the c-*KIT* mutation site directly affects the clinical response to regorafenib, it should be considered that different exons encode different domains: exon 9 encodes part of the extracellular domain, exon 11 encodes the intracellular juxtamembrane domain, exons 13 and 14 encode the adenosine triphosphate-binding pocket, and exons 17 and 18 encode the kinase activation loop [26–28]. Regorafenib exerts its anticancer activity through competitive inhibition of the adenosine triphosphate-binding site for KIT and other targets, including *VEGFR*, *PDGFR*, *FGFR*, *RET*, and *RAF* [11]. In previous *in vitro* studies using GIST cell lines, regorafenib showed comparable half-maximal inhibitory concentration (IC_{50}) values (35–150 nM) to imatinib (4.5–35 nM), sunitinib (5–10 nM), sorafenib (30–40 nM), and nilotinib (15–50 nM) for exon 11 mutations. By contrast, regorafenib has relatively higher efficacy against exon 13 and exon 17 mutations, which usually arise as secondary mutations associated with resistance to imatinib [29]. Previous clinical trials of regorafenib therapy for patients with exon 17 mutation-specific GIST who had been previously treated with imatinib support these findings [30,31].

Previous studies on imatinib, nilotinib, and ripretinib have consistently reported favourable outcomes in the subset of patients harbouring c-*KIT* exon 11 mutations [19–22,25]. Contrary to these results, our findings showed that the patients in the exon 11 mutation group had similar ORR and DCR, but shorter OS and PFS, than those seen in the non-exon 11 mutation group. Differing regorafenib sensitivities at different mutation

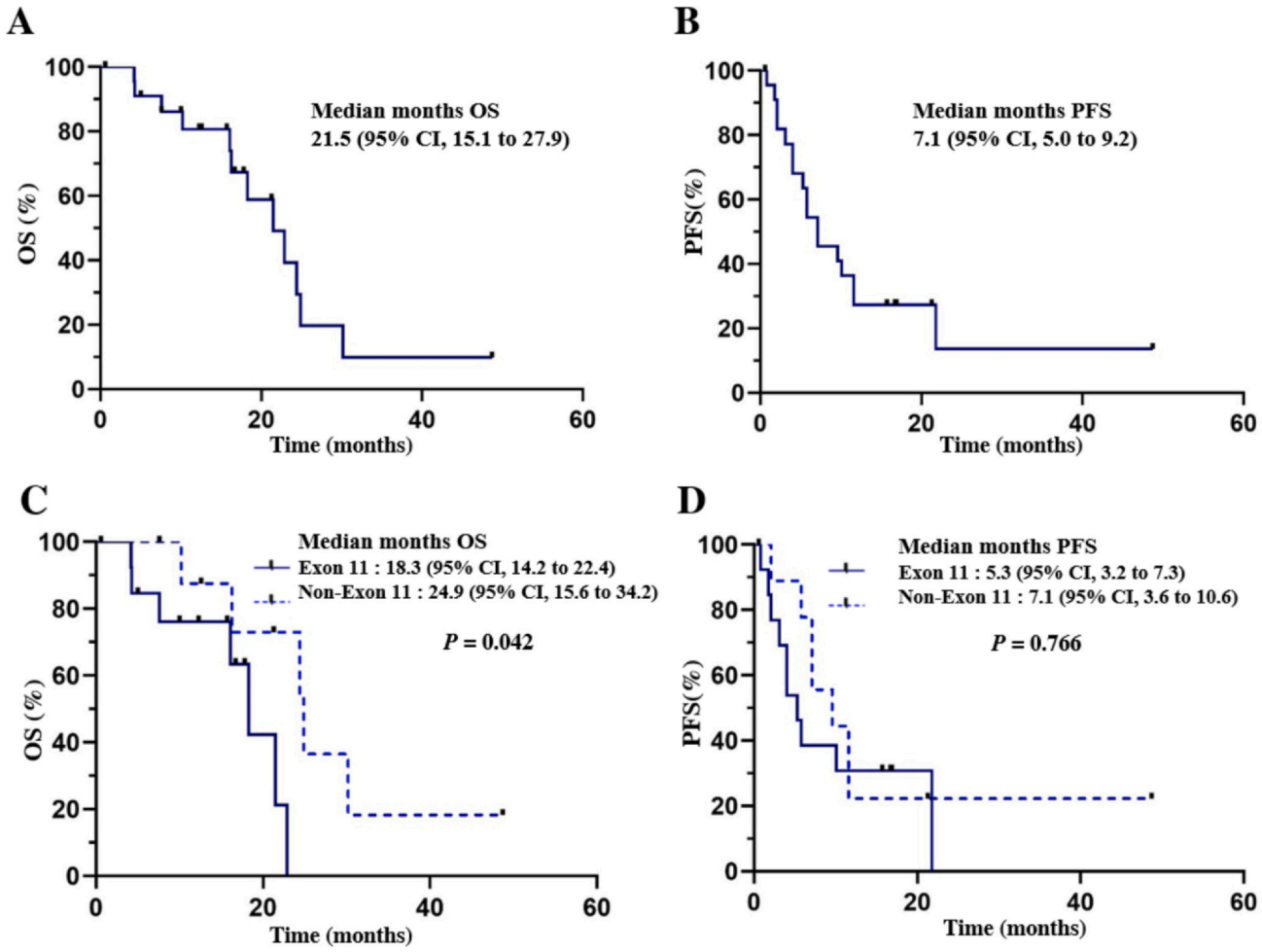

Fig. 2. Kaplan–Meier survival curves (A) Overall survival (OS). (B) Progression-free survival (PFS). (C) OS of exon 11 versus non-exon 11 mutation groups. (D) PFS of exon 11 versus non-exon 11 mutation groups.

sites may play a key role in its efficacy, and tumour heterogeneity may also play a partial role [31].

We also attempted to validate the role of liquid biopsy in detecting c-*KIT* mutations, as the patients enrolled already had known c-*KIT* mutations as part of the inclusion criteria. Liquid biopsy is a less invasive alternative to conventional biopsy for detecting ctDNA in the blood, and the possibility of using liquid biopsy for screening/monitoring of metastatic disease or disease progression has already been suggested [32–36]. Due to the small sample size, we could not reach a robust conclusion on the reliability of plasma-based c-*KIT* monitoring; in cases wherein c-*KIT* mutations were detected, there was a high correlation (85.7%) between the tumour and plasma mutation profiles.

Regarding safety and AEs, PPE was the most commonly reported adverse effect, although with mild-to-moderate severity. Grade 3 events including skin rash other than PPE were reported in 39.1% of patients. AEs were generally tolerable and managed with dose interruption, followed by dose reduction. These findings are consistent with those of other studies on the c-*KIT*-targeting agent imatinib as well as on regorafenib for other solid cancers [37].

The current study has several limitations. Despite its prospective design, the potential of selection bias inherent to the single-arm study design cannot be ignored. Serial blood sampling was not consistent throughout the study, and consequently, only a few paired samples from the baseline and time of disease progression were available for exploratory analysis. Lastly, patient accrual was difficult given the low positive screening rate of approximately 20%, resulting in the enrolment of fewer patients than originally planned. Further analysis of the underlying molecular mechanisms and a larger cohort of patients with melanoma patients harbouring c-*KIT* mutations are warranted to validate and support our findings.

Table 4
Incidence of treatment-related adverse events.

	All grades		Grade 3	
	No	%	No	%
Haematologic				
Thrombocytopenia	3	13.0	1	4.3
Neutropenia	2	8.7	1	4.3
Anaemia	1	4.3	0	0
Pancytopenia	1	4.3	0	0
Non-haematologic				
Palmar-plantar erythrodysesthesia	12	52.2	0	0
Skin rash	7	30.4	3	13.0
Anorexia	5	21.7	0	0
General Weakness	3	13.0	0	0
Hypertension	3	13.0	0	0
Mucositis	3	13.0	0	0
Myalgia	3	13.0	0	0
Diarrhoea	3	13.0	0	0
Abdominal pain	2	8.7	0	0
Dyspepsia	2	8.7	0	0
Infection	2	8.7	2	8.7
Fatigue	2	8.7	1	4.3
Neuropathy	2	8.7	0	0
Dyspnoea	2	8.7	0	0
AST elevation	2	8.7	1	4.3
ALT elevation	1	4.3	0	0
Gastritis	1	4.3	0	0
Visual disturbance	1	4.3	0	0
Headache	1	4.3	0	0
Weight loss	1	4.3	0	0
Dizziness	1	4.3	0	0
Cr elevation	1	4.3	0	0
Nausea	1	4.3	0	0
Vomiting	1	4.3	0	0
Hypoalbuminemia	1	4.3	1	4.3
Alopecia	1	4.3	0	0
Hoarseness	1	4.3	0	0
Asthenia	1	4.3	0	0
Hypocalcemia	1	4.3	0	0
Amenorrhea	1	4.3	0	0
Fever	1	4.3	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, Creatinine

5. Conclusion

In the second- or later-line setting, regorafenib therapy demonstrated significant activity in patients with metastatic melanoma harbouring c-*KIT* mutations, with an ORR of 30.4% and DCR of 73.9%. AEs were consistent in frequency and severity with known safety profile. Our data establish that regorafenib should be considered as a treatment option for selected patients. However, additional investigations on the role of ctDNA are needed in the future.

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CRediT authorship contribution statement

Kyoo Hyun Kim: Formal analysis, Writing – Original draft preparation, Visualization. **Minkyu Jung**: Conceptualization, Methodology, Investigation, Resources, Project administration, Funding acquisition, Writing – review & editing. **Hyo Jin Lee**: Investigation, Resources, Writing – review & editing. **Su Jin Lee**: Investigation, Resources, Writing – review & editing. **Miso Kim**: Investigation, Resources, Writing – review & editing. **Mi Sun Ahn**: Investigation, Resources, Writing – review & editing. **Moon Young Choi**: Investigation, Resources, Writing – review & editing. **Na-Ri Lee**: Investigation, Resources, Writing – review & editing. **Sang Joon Shin**: Investigation, Resources, Writing – review & editing, Supervision, Project administration.

Table 5
Comparisons of studies using target agents against c-*KIT* in malignant melanoma.

Trial	Phase	Trial drug	Patient	mPFS (Months)	mOS (Months)	ORR (%)	DCR (%)
			number	(95% CI)	(95% CI)		
Carvajal et al. 2011[3]	II	imatinib	28	2.8 (2.5–4.0)	10.7 (6.5-NR)	24.0	44.0
Guo et al. 2011[9]	II	imatinib	43	3.5 (1.3–5.7)	14.0 (10.8–17.2)	23.3	53.5
Hodi et al. 2013[10]	II	imatinib	24	3.7 (2.6–5.6)	12.5 (8.8–18.0)	29.2	50.0
KIT mutation subgroup			13	3.9 (2.6–6.6)	12.9 (5.5–24.3)	53.8	76.9
KIT amplification subgroup			11	3.4 (1.0–5.7)	11.9 (4.5–16.2)	0.0	18.2
Lee et al. 2015[22]	II	nilotinib	42	3.3 (1.6–4.9)	11.9 (7.1–16.7)	16.7	57.1
Guo et al. 2017[21]	II	nilotinib	42	4.2 (2.1–5.8)	18.0 (10.9–20.3)	26.2	47.6
Deylon et al. 2018[19]	II	nilotinib	25	6.0 (3.0–11.2)	13.2 (8.9–22.3)	20.0	56.0
Janku et al. 2022[20]	I	ripretinib	26	7.3 (1.9–13.6)	-	23.0	-
Regorafenib (current study)	II	regorafenib	23	7.1 (5.0–9.2)	21.5 (15.1–27.9)	30.4	73.9

PFS, progression-free survival; OS, overall survival; ORR, overall response rate; DCR, disease control rate; NR, not reached.

Data availability

The datasets used and/or analysed during the study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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IRB approval status

This study was conducted according to the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki and in the ICH Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Review Boards of each participating centre. All eligible participants had the study, timelines, and outcome measures of the study explained to them. Participants were informed that they were free to discontinue participation at any time without consequence. All participants provided written informed consent.

ClinicalTrials.gov: NCT02501551.

Patient consent on file

Consent for the publication of recognisable patient photographs or other identifiable material was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113312.

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