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# Safety and efficacy of pertuzumab and trastuzumab in patients with HER2-Positive metastatic colorectal cancer: comparison of intravenous and subcutaneous formulations.

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**Research Article**

**Keywords:** HER2-positive mCRC, pertuzumab and trastuzumab, injection- or infusion-related reactions (IRRs)

**Posted Date:** September 4th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-10623924/v1

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## Abstract

# Background

Pertuzumab plus trastuzumab is an established treatment for HER2-positive metastatic colorectal cancer (mCRC). While efficacy and safety of the intravenous (IV) formulation have been established, data on the subcutaneous (SC) formulation remain limited. This study compared the safety and efficacy of IV and SC pertuzumab and trastuzumab.

# Methods

We retrospectively compared the efficacy, safety, and treatment process time of IV and SC pertuzumab and trastuzumab in patients with HER2-positive mCRC.

# Results

Thirty-six patients were included (17 received the IV formulation and 19 received the SC formulation). No patients switched formulations during the treatment period. The ORR was 26.3% in the SC group and 23.5% in the IV group, while the DCR was 73.7% and 70.6%, respectively. Regarding safety, the incidence of IRRs was numerically lower in the SC group than in the IV group (15.8% [3/19] and 47.1% [8/17], respectively; $p = 0.070$). Rash and pruritus occurred at similar frequencies between the IV and SC groups (11.8% [2/17] vs. 10.5% [2/19] and 5.9% [1/17] vs. 10.5% [2/19], respectively). Injection site reactions occurred only in the SC group (10.5% [2/19] vs. 0% [0/17]). The median treatment process time was 97.5 minutes in the SC group and 208.0 minutes in the IV group ($p < 0.001$).

# Conclusions

The SC formulation showed efficacy comparable to that of the IV formulation with a lower incidence of IRRs and a substantially shorter treatment process time. These findings suggest that the SC formulation is a feasible and convenient alternative to IV administration in clinical practice.

## Introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 2–4% of colorectal cancers (CRC) and has been associated with resistance to anti-epidermal growth factor receptor (EGFR) antibody therapy [1, 2]. The TRIUMPH study, a multicenter phase II trial conducted in Japan, demonstrated the efficacy of pertuzumab plus trastuzumab in patients with HER2-positive unresectable advanced or recurrent CRC (mCRC) [3]. Similarly, the international phase II MyPathway basket study reported an objective response rate (ORR) of 32%, a median progression-free survival (PFS) of 2.9 months, and a median overall survival (OS) of 11.5 months among 57 evaluable patients with HER2-

positive mCRC treated with the same combination [4]. Based on these findings, the combination of pertuzumab and trastuzumab has emerged as a promising treatment option for patients with HER2-positive mCRC who have received prior chemotherapy and was subsequently approved in Japan.

The fixed-dose subcutaneous (SC) formulation of pertuzumab and trastuzumab was developed to simplify administration and improve treatment convenience. In the phase III FeDeriCa trial in patients with HER2-positive early breast cancer, the SC formulation of pertuzumab and trastuzumab demonstrated non-inferior pharmacokinetics, comparable efficacy and safety to intravenous (IV) administration [5]. These results supported its approval in Japan in February 2024, after which it became available for clinical use in patients with HER2-positive mCRC.

Although the efficacy and safety of dual HER2 blockade with pertuzumab plus trastuzumab has been established in HER2-positive mCRC, date on the SC formulation in this population remain limited. In particular, injection- or infusion- related reactions (IRRs), which are hypersensitivity reactions associated with antibody-based therapies, remain an important safety concern, as they may be severe or even life-threatening in a small number of cases. Previous studies of the IV formulation reported IRR rates of 26.9% in the CLEOPATRA trial and 46.7% in the TRIUMPH study, suggesting that the incidence of IRRs may vary across tumor types [3, 6]. However, the incidence and clinical characteristics of IRRs associated with the SC formulation in patients with HER2-positive mCRC have not been well characterized, and direct comparisons between the IV and SC formulations are lacking.

Therefore, this study aimed to compare the efficacy, safety, and treatment convenience of IV and SC formulations of pertuzumab and trastuzumab in patients with HER2-positive mCRC, with a particular focus on IRRs.

## Patients and Methods

# Study design and patients

We retrospectively analyzed clinical outcomes in patients with HER2-positive mCRC treated with IV or SC pertuzumab and trastuzumab at National Cancer Hospital East (Kashiwa, Japan) between March 2022 and March 2026. HER2 positivity was defined as overexpression of the HER2 protein (immunohistochemistry (IHC) score 3+), *ERBB2* amplification confirmed by fluorescence in situ hybridization (FISH) in cases with IHC score 2+, or *ERBB2* amplification identified by liquid biopsy-based next-generation sequencing (NGS), according to institutional testing practices.

## Treatment regimen

All patients received either SC or IV pertuzumab and trastuzumab. The formulation was determined according to the treatment period. Before the introduction of the SC formulation at our institution, all patients received the IV formulation. After the SC formulation became available, all eligible patients

received the SC formulation. No patients switched formulations during the treatment period. In the IV group, pertuzumab was administered intravenously at a loading dose of 840 mg followed by 420 mg every 3 weeks, and trastuzumab was administered at a loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks. In the SC group, patients received a subcutaneous formulation of pertuzumab and trastuzumab consisting of pertuzumab 1,200 mg and trastuzumab 600 mg for the initial dose, followed by pertuzumab 600 mg and trastuzumab 600 mg every 3 weeks, administered subcutaneously into the thigh.

## Outcomes

Progression-Free Survival (PFS) was defined as the time from the initiation of study treatment to disease progression or death from any cause. Objective response rate (ORR) was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the proportion of patients achieving CR, PR, or stable disease (SD). Tumor response was assessed by investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. IRRs were defined as signs or symptoms occurring during or within 24 hours after administration and considered related to treatment. Treatment process time was defined as the time from physician order confirmation to completion of drug administration. The analysis of treatment process time excluded patients receiving the first administration and those who received treatment during hospitalization.

# Statistical analysis

Group comparisons were conducted using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test or Student's *t*-test for continuous variables, as appropriate. Progression-free survival (PFS) was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Median PFS and corresponding 95% confidence intervals (CIs) were calculated. Treatment process time was summarized as the median and compared between groups using the Wilcoxon rank-sum test. All statistical tests were two-sided, and a $p$-value $< 0.05$ was considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

## Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the National Cancer Center Hospital East (approval number #2024 – 117). The requirement for informed consent was waived due to the retrospective nature of the study, and an opt-out approach was used.

## Results

# Patient characteristics

A total of 36 patients with HER2-positive mCRC who received pertuzumab and trastuzumab were included in this study, comprising 17 patients in the IV group and 19 patients in the SC group. No patients switched formulations during the treatment period. Baseline patient characteristics are summarized in Table 1. The median age was 57 years (range, 26–79) in the IV group and 66 years (range, 42–85) in the SC group, with no statistically significant difference ($p = 0.138$), although patients aged ≥ 65 years were more frequently treated with the SC formulation (47.4% vs. 82.4%, $p = 0.041$). Regarding metastatic sites, lung metastases were more frequently observed in the IV group than in the SC group (88.2% vs. 21.1%, $p < 0.001$). Regarding HER2 status, HER2 positivity by IHC/FISH was confirmed in 70.6% of patients in the IV group and 94.7% in the SC group, whereas ERBB2 amplification by NGS was detected in 64.7% and 26.3%, respectively. HER2 positivity confirmed by both IHC/FISH and ERBB2 amplification by NGS was observed in 35.3% of patients in the IV group and 21.1% in the SC group. The median number of previous treatment regimens also differed between the groups, with a greater proportion of patients receiving three or more prior regimens in the IV group (88.2% vs. 52.6%, $p = 0.031$). No patients had obesity(BMI ≥ 30 kg/m²), and all patients had advanced-stage disease.

Table 1
Patient characteristics.

| **Median age at treatment (range)** | **SC (n = 19)** | **IV (n = 17)** | ***P* - value** |
|---|---|---|---|
| | **66.0 (42–85)** | **57.0 (26–79)** | **0.138** |
| Age < 65 | 9 (47.4%) | 14 (82.4%) | 0.041 |
| Sex | | | 0.730 |
| Male | 13 (68.4%) | 10 (58.8%) | |
| BMI, kg/$m^2$, median (range) | 22.3 (14.4–29.9) | 22.2 (17.2–29.1) | 0.802 |
| BMI ≥ 30kg/$m^2$ | 0 (0.0%) | 0 (0.0%) | |
| ECOG PS | | | 1.000 |
| 0 | 12 (63.2%) | 11 (64.7%) | |
| 1 | 6 (31.5%) | 6 (35.3%) | |
| 2 | 1 (5.3%) | 0 (0.0%) | |
| Left | 17 (89.5%) | 15 (88.2%) | 1.000 |
| Number of metastatic sites | | | 0.487 |
| 1 | 2 (10.5%) | 0 (0.0%) | |
| ≥2 | 17 (89.5%) | 17 (100.0%) | |
| Site of metastasis | | | |
| Liver | 13 (68.4%) | 16 (94.1%) | 0.284 |
| Lung | 4 (21.1%) | 15 (88.2%) | < 0.001 |
| Lymph | 6 (31.6%) | 10 (58.8%) | 0.071 |
| Peritoneal | 3 (15.8%) | 4 (23.5%) | 0.684 |
| HER2 status | | | |
| IHC/FISH positive | 18 (94.7%) | 12 (70.6%) | 0.081 |
| ERBB2 amplification (NGS) | 5 (26.3%) | 11 (64.7%) | 0.043 |
| Number of previous regimens | | | 0.031 |
| ≤2 | 9 (47.4%) | 2 (11.8%) | |

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; ERBB2, erb-b2 receptor tyrosine kinase 2.

| Median age at treatment (range) | SC (n = 19) | IV (n = 17) | *P* - value |
|---|---|---|---|
| | **66.0 (42–85)** | **57.0 (26–79)** | **0.138** |
| ≥3 | 10 (52.6%) | 15 (88.2%) | |

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; ERBB2, erb-b2 receptor tyrosine kinase 2.

## Safety

Treatment-related adverse events (TRAEs) were observed in 13 of 19 patients (68.4%) in the SC group and 15 of 17 patients (88.2%) in the IV group. No grade ≥ 3 TRAEs were observed in either group. The most common TRAEs were diarrhea (30.6%), IRRs (30.6%), Fatigue (22.2%), rash and pruritus (19.4%), and injection site reactions (5.6%) (Table 2). IRRs occurred only during the first administration in both groups. The incidence of IRRs was numerically lower in the SC group than in the IV group (3/19 [15.8%] vs. 8/17 [47.1%]; $p = 0.070$). All IRRs were grade 1 or 2 and resolved with supportive management, including temporary interruption or slowing of the infusion, administration of antipyretics and corticosteroids, or observation alone, with no permanent treatment discontinuation (Table 3). The incidences of rash and pruritus were similar between the IV and SC groups (11.8% [2/17] vs. 10.5% [2/19] and 5.9% [1/17] vs. 10.5% [2/19], respectively). Injection site reactions occurred only in the SC group (10.5% [2/19] vs. 0% [0/17]). Premedication was administered to all patients in the IV group, whereas only seven patients in the SC group received prophylactic medication (prednisolone 10 mg, acetaminophen 500 mg, and loratadine 10 mg). In the SC group, premedication consisted of prednisolone, acetaminophen, and loratadine, Notably, no IRRs occurred among the patients in the SC group who received premedication; all IRRs occurred in patients who did not receive premedication.

Table 2
Incidence of adverse events.

| | All Grade | | | | ≥Grade3 | | |
|---|---|---|---|---|---|---|---|
| | **All (n = 36, %)** | **SC (n = 19, %)** | **IV (n = 17, %)** | ***P* - value** | **All (%)** | **SC (%)** | **IV (%)** |
| All adverse events | 28 (77.8%) | 13 (68.4%) | 15 (88.2%) | 0.236 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Diarrhea | 11 (30.6%) | 6 (31.6%) | 5 (35.3%) | 0.855 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| IRR | 11 (30.6%) | 3 (15.8%) | 8 (47.1%) | 0.070 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Fatigue | 8 (22.2%) | 2 (10.5%) | 6 (35.3%) | 0.114 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Rash | 4 (11.1%) | 2 (10.5%) | 2 (11.8%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pruritus | 3 (8.3%) | 2 (10.5%) | 1 (5.9%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Injection site reaction | 1 (2.8%) | 1 (5.3%) | 0 (0.0%) | 0.487 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Nausea | 3 (8.3%) | 1 (5.3%) | 2 (11.8%) | 0.593 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Constipation | 1 (2.8%) | 1 (5.3%) | 0 (0.0%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hepatotoxicity | 2 (5.6%) | 1 (5.3%) | 1 (5.9%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypokalemia | 1 (2.8%) | 1 (5.3%) | 0 (0.0%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Paronychia | 1 (2.8%) | 1 (5.3%) | 0 (0.0%) | 1.000 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Appetite loss | 2 (5.6%) | 0 (0.0%) | 2 (11.8%) | 0.216 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Stomatitis | 2 (5.6%) | 0 (0.0%) | 2 (11.8%) | 0.216 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

IRR, injection- or infusion-related reaction; Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Table 3
Distribution of IRR and Corresponding Coping Strategies.

| Group | Adverse events | Grade | Coping strategy |
|---|---|---|---|
| SC | Fever | 1 | Observed |
| SC | Fever | 1 | Observed |
| SC | Chills | 1 | Observed |
| IV | Fever | 1 | Antipyretics and steroids were administered, and the infusion rate was reduced |
| IV | Chills | 2 | Antipyretics and steroids were administered, and the infusion rate was reduced |
| IV | Chills | 2 | Antipyretics and steroids were administered, and the infusion rate was reduced |
| IV | Chills | 2 | Antipyretics and steroids were administered, and the infusion rate was reduced |
| IV | Chills | 1 | Antipyretics were administered. |
| IV | Fever, Chills | 1 | Antipyretics were administered. |
| IV | Fever | 1 | Antipyretics were administered. |
| IV | Fever | 1 | Antipyretics were administered. |

# Efficacy and Treatment efficiency

The median PFS was 3.91 months (95% CI, 1.81–5.75) in the IV group and 5.49 months (95% CI, 2.53–6.93) in the SC group, with no significant difference between the groups (HR 0.79, 95% CI 0.38–1.62; log-rank $p = 0.516$) (Fig. 1). After adjustment for number of previous treatment lines, the difference remained not significant (adjusted HR 0.91, 95% CI 0.42–1.98; $p = 0.804$). The ORR was 23.5% in the IV group and 26.3% in the SC group ($p = 1.000$). The DCR was 70.6% in the IV group and 73.7% in the SC group, with no statistically significant difference between the groups ($p = 1.000$) (Table 4, Fig. 2). The median treatment process time was significantly shorter in the SC group than in the IV group (97.5 minutes vs. 208.0 minutes, $p < 0.001$) (Fig. 3).

Table 4
tumor response rate.

| **ORR (%)** | **SC(n = 19)** | **IV(n = 17)** | ***P* - value** |
|---|---|---|---|
| | **26.3%** | **23.5%** | **1.000** |
| DCR (%) | 73.7% | 70.6% | 1.000 |
| CR | 0 (0.0%) | 0(0.0%) | |
| PR | 5 (26.3%) | 4 (23.5%) | |
| SD | 9 (47.4%) | 8 (47.1%) | |
| PD | 5 (26.3%) | 5 (29.4%) | |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

# Discussion

In this study, the SC formulation of pertuzumab and trastuzumab demonstrated safety and efficacy profile comparable to those of the IV formulation in patients with HER2-positive mCRC. Furthermore, SC administration was associated with a markedly shorter treatment process time, supporting its potential to improve the efficiency of outpatient cancer care. To date, the efficacy and safety of the SC formulation have been primarily evaluated in the PHranceSCa and FeDeriCa trials conducted in patients with HER2-positive breast cancer. Our findings suggest that the SC formulation may also represent a potential treatment option for HER2-positive mCRC. In addition, the SC formulation is administered over a shorter duration than the IV formulation (at least 8 minutes for the initial dose and 5 minutes for subsequent doses), which may contribute to a reduction in patient burden and improved treatment efficiency. In the present study, treatment process time was significantly shorter in the SC group than in the IV group (97.5 min vs. 208.0 min, $p < 0.001$), indicating that SC administration may reduce not only administration time but also the overall time spent in the outpatient chemotherapy unit. This reduction may help alleviate patient burden, improve patient throughput, and optimize workflow in outpatient oncology settings, reduce the workload of healthcare professionals, and enable more efficient use of healthcare resources.

The overall safety profiles of the SC and IV formulations were comparable, and no grade ≥ 3 TRAEs were observed in either group. Notably, the incidence of IRRs was numerically lower in the SC group than in the IV group. This finding is consistent with previous studies, including the FeDeriCa and PHranceSCa trials, which reported a lower incidence of IRRs with SC administration [5, 7]. The lower incidence of IRRs with the SC formulation may be attributable to differences in administration route and pharmacokinetics. Subcutaneous administration results in slower absorption and a more gradual increase in serum drug concentration, leading to a lower peak concentration (Cmax) compared with intravenous administration [8], which may reduce the likelihood of acute immune-mediated reactions [9]. In addition, the use of recombinant hyaluronidase facilitates drug dispersion in the subcutaneous tissue, contributing to a more

stable pharmacokinetic profile [10]. Furthermore, differences in premedication strategies between the two groups may have influenced the incidence of IRRs. Considering the relatively high incidence of IRRs reported in the TRIUMPH study, seven of the first 19 patients who received the SC formulation at our institution were given prophylactic premedication with prednisolone 10 mg, acetaminophen 500 mg, and loratadine 10 mg before treatment. None of these patients experienced an IRR. Although the sample size was limited and the use of premedication was not standardized, this finding suggests that prophylactic premedication may have contributed to the lower incidence of IRRs observed in the SC group.

However, our findings do not support the routine administration of premedication to all patients receiving the SC formulation. Previous studies of intravenous trastuzumab have identified several potential risk factors for IRRs, including obesity (BMI ≥ 30 kg/m²) and advanced-stage disease [11]. In the present study, no patients in had obesity, and all patients had advanced-stage disease; therefore, the applicability of these reported risk factors could not be evaluated in our cohort. As the risk factors for trastuzumab-related IRRs have been established primarily in patients receiving the IV formulation, further studies are warranted to determine whether these risk factors are also applicable to the SC formulation and to identify patients who may benefit from selective prophylactic premedication. Importantly, all IRRs in the present study were grade 1 or 2 and resolved with supportive management, indicating that these events were generally mild and manageable.

In terms of efficacy, no significant differences were observed in PFS, ORR, or DCR between the SC and IV groups. These findings are consistent with previous studies demonstrating non-inferior efficacy of SC administration. Although cross-study comparisons should be interpreted cautiously, our results suggest that changing the route of administration does not compromise antitumor activity in HER2-positive mCRC.

This study has several limitations. First, it was a retrospective, single-center study with a relatively small sample size, which may limit generalizability. Second, baseline characteristics differed between the two groups may have influenced the results. Third, differences in HER2 testing methods and premedication strategies may have introduced bias.

# Conclusion

The SC formulation of pertuzumab and trastuzumab demonstrated comparable efficacy and safety to the IV formulation in patients with HER2-positive mCRC, with a lower incidence of IRRs and significantly improved treatment efficiency. These results support the clinical utility of SC administration as a convenient and effective alternative to IV administration in clinical practice.

# Declarations

**ACKNOWLEDGMENT**We thank the patients and their families for their participation in this study. We also thank the clinical and research staff at the National Cancer Center Hospital East for their support.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

S. Mishima:

Honoraria from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Eli Lilly Co., Ltd.

A. Kawazoe reports grants from Abbvie, AstraZeneca and MSD; consulting fees from Zymeworks, MSD, Revolution Medicines, and Abbvie; honoraria from Taiho Pharmaceutical, Bristol Myers Squibb (BMS), Merck Serono, Ono, and Daiichi Sankyo; support for attending meetings or travel from Ono and MSD; and participation on an advisory board in Abbvie.

Y. Matsubara:

Honoraria from Chugai and MSD.T. Hashimoto:

honoraria from CytoGen, Myriad Genetics, Miyarisan Pharmaceutical, Guardant Health, Takeda Pharmaceutical, Chugai Pharmaceutical and Takata Pharmaceutical; and consulting and advisory roles from Guardant Health.

I. Nakayama: Research funding from Astellas, Ono Pharmaceutical Co., Ltd., Merck Sharp & Dohme (MSD), Daiichi Sankyo, Boehringer Ingelheim, AstraZeneca, and Chugai Pharmaceutical Co., Ltd. Honoria from Astellas, Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, Merck Sharp & Dohme (MSD), Daiichi Sankyo, and AstraZeneca.D. Kotani:

Honoraria from Takeda, Chugai, Lilly, MSD, Ono, Taiho, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Eisai, and Merck Biopharma

Research funding from Ono, MSD, Novartis, Servier, Janssen, IQVIA, Syneos Health, Cimic, and Cimicshiftzero

Y. Kuboki:

Advisory roles (personal fees) from Taiho, Takeda, and Boehringer Ingelheim

Honoraria from Taiho, Ono, Bayer, and Sanofi

Institutional grants or contracts from Taiho, Takeda, Ono, AbbVie, AstraZeneca, Boehringer Ingelheim, Incyte, Amgen, Chugai, GlaxoSmithKline, Genmab, Astellas, and Daiichi Sankyo

H. Bando:

Research funding from Ono Pharmaceutical

Honoraria from Ono Pharmaceutical, Taiho Pharmaceutical, and Guardant Health

T. Kojima:

Honoraria as invited speaker and for manuscript writing from Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., Covidien Japan, Inc., MSD K.K., Taiho Pharmaceutical Co., Ltd., and Oncolys BioPharma Inc.

Research funding from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, BeiGene Ltd., EPS Corporation, MSD K.K., Amgen Inc., Shionogi & Co., Ltd., and Chugai Pharmaceutical Co., Ltd.

T. Yoshino:

Honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Merck Biopharma, and Ono Pharmaceutical

Consulting fee from Sumitomo Corp. and Indivumed.

Research funding from Bristol-Myers, Caris, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Exact Sciences, FALCO Biosystems, Medical & Biological Laboratories, Merus N.V., MSD, Miyarisan, Natera, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer, Sysmex, Taiho Pharmaceutical, and Takeda Pharmaceutical.

K. Shitara reports receiving personal fees for consulting and advisory roles from
Bristol Myers Squibb, Takeda, Ono Pharmaceutical, Novartis, Daiichi Sankyo, Amgen, Boehringer Ingelheim, Merck Pharmaceutical, Astellas, Guardant Health Japan, Janssen, AstraZeneca, Zymeworks Biopharmaceuticals, ALX Oncology Inc., Bayer, GlaxoSmithKline K.K., HEALIOS K.K., Moderna.Inc, Arcus Biosciences Inc, Abbvie, CMIC co.,Ltd, Elevation Oncology, Oncolys BioPharma, Sanofi, Suzuhou Lingyhui Network Technology, Giliad Science, eChinaHealth, Leap Therapeutics, Phans Therapeutics, Scandion Oncology, and Revolution Medicines; receiving honoraria from Bristol-Myers Squibb, Ono Pharmaceutical, Janssen, Eli Lilly, Astellas, and AstraZeneca; and receiving research funding (all to institution) from
Astellas, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Chugai, Merck Pharmaceutical, Amgen, Eisai, PRA Health Sciences, Syneos Health, AstraZeneca, PPD-SNBL K.K. TORAY, Insyte Biosciences G.K, and Medpace Japan K.K

All remaining authors have no competing interests to declare.

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# Figures

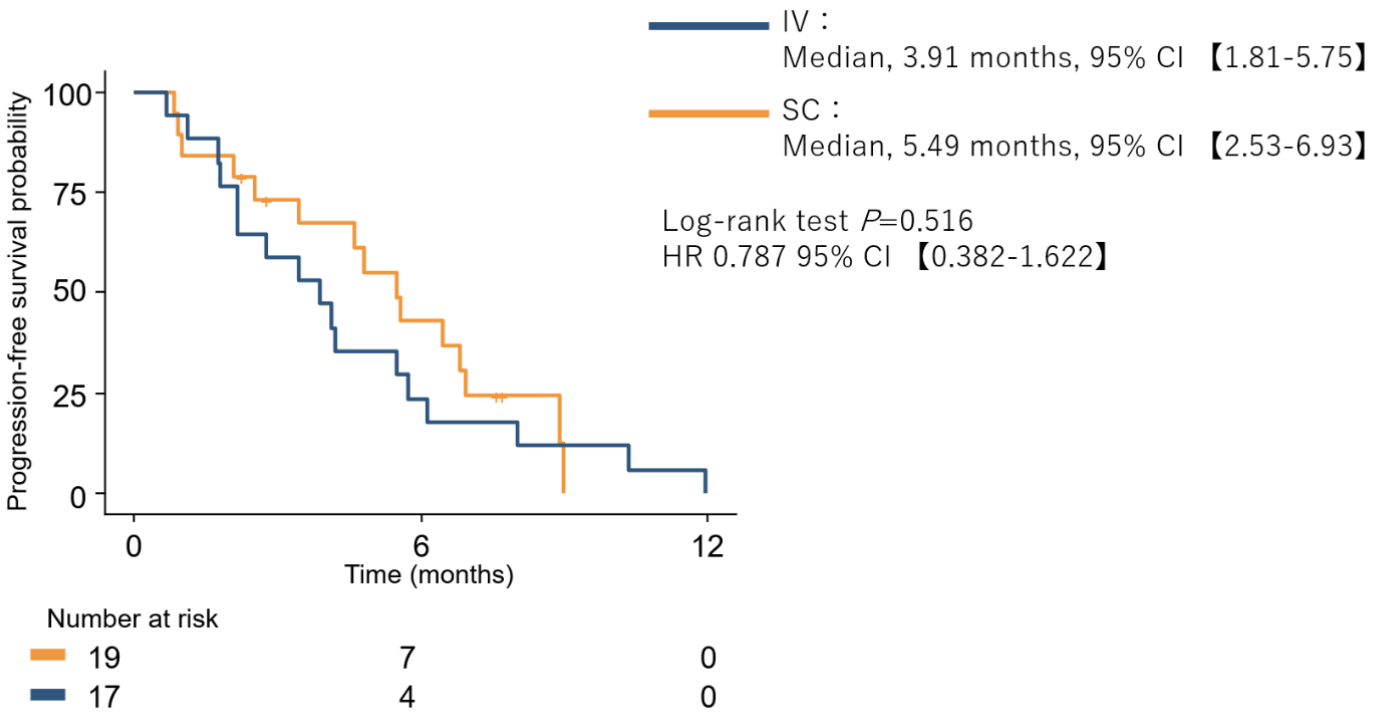



**Figure 1**

**Kaplan–Meier survival curves of progression-free survival according to administration route.**
PFS according to IV (n = 17) and SC (n = 19) administration. Median PFS was 3.91 months in the IV group and 5.49 months in the SC group. The P value was calculated using the log-rank test. The HR and 95% CI were estimated using univariable Cox proportional-hazards regression.
PFS, progression-free survival; IV, intravenous; SC, subcutaneous; HR, hazard ratio; CI, confidence interval.

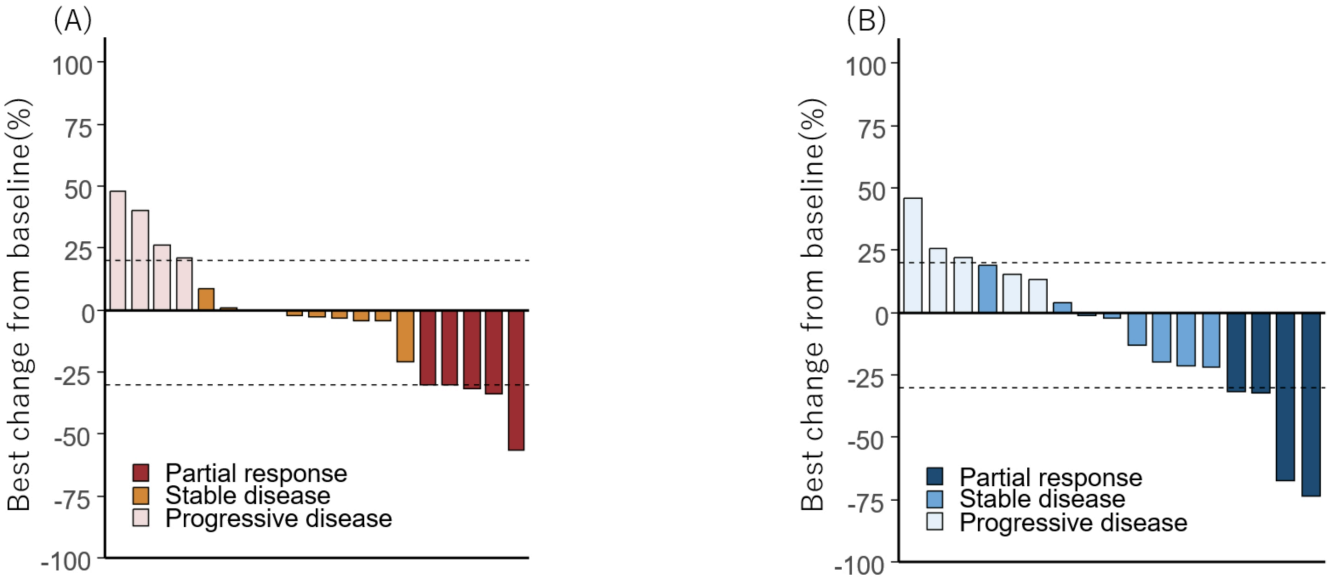



**Figure 2**

**Waterfall plots of the best percentage change from baseline in tumor size in the SC and IV groups.**
Waterfall plots showing the best percentage change from baseline in the sum of target lesion diameters in the SC (A) and IV (B) groups. Each bar represents an individual patient and is colored according to the best overall response assessed by RECIST version 1.1. The dashed lines indicate the thresholds for progressive disease (+20%) and partial response (−30%).
SC, subcutaneous; IV, intravenous; RECIST, Response Evaluation Criteria in Solid Tumors.

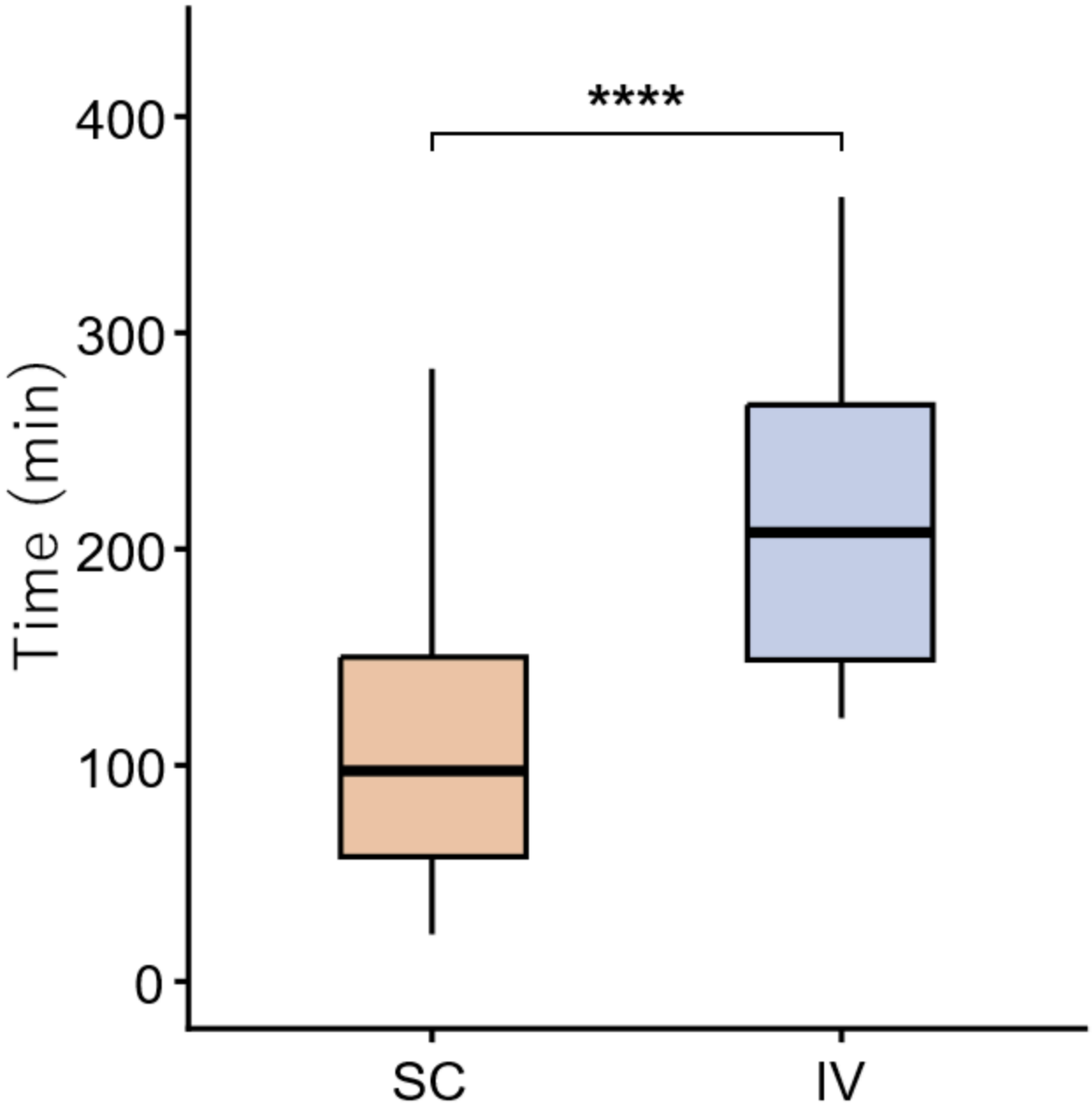



**Figure 3**

**Comparison of median treatment process time between the subcutaneous (SC) and intravenous (IV) formulations.**

Box plots show the median and interquartile range, with whiskers indicating the range excluding outliers. Individual outliers are plotted as points. The SC formulation was associated with a significantly shorter preparation-to-administration time compared with the IV formulation ($p < 0.001$, Wilcoxon rank-sum test).