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Clinical Trial Results

Safety and Efficacy of Bis-Glyceryl Ascorbate as Prophylaxis for Hand-Foot Skin Reaction: A Single-Arm, Open-Label Phase I/II Study (DGA Study)

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Abstract

Background: Hand-foot skin reaction (HFSR) induced by multiple tyrosine kinase inhibitors (TKIs) is a serious side effect that can cause treatment interruption or decreased dosing. This study was conducted to evaluate the safety and efficacy of bis-glyceryl ascorbate (Amitose bis(di)-glyceryl ascorbate [DGA])-containing cream (DGA cream) for the prevention of sunitinib-induced HFSR.

Methods: A single-arm, open-label phase I/II study was conducted, targeting patients with metastatic renal cell carcinoma (mRCC) who were receiving sunitinib therapy with a schedule of 2 weeks on/1 week off. The participants applied DGA cream to both palmar and plantar surfaces in combination with a moisturizing agent as standard-of-care prophylaxis during two sunitinib treatment cycles (6 weeks). The primary endpoint in phase I was safety defined as dermatological abnormalities and it was determined in the first five participants. The primary endpoint in phase II was efficacy defined as development of grade 1 or higher HFSR defined by Common Terminology Criteria for Adverse Events within 6 weeks and it was determined on a full analysis set (FAS) defined as the population including all participants who used DGA cream once in the study duration. Efficacy in the per protocol set (PPS) defined as the population excluding seven patients whose study treatment was interrupted was evaluated as a secondary endpoint.

Results: Twenty-four patients were enrolled as a FAS. No dermatological abnormalities occurred in the first 5 patients enrolled in the phase I study. Three patients developed HFSR (grade 1: $n = 2$, grade 2: $n = 1$) in the observation period. The HFSR incidence rate was 12.5% (3/24; 95% confidence interval [CI]: 2.7%-32.4%) in the FAS, which was significantly lower than the incidence rate predefined as a threshold of 33.3% by a previous report from our hospital ($P = .030$). The incidence rate in the 17 patients of the PPS was 17.6% (3/17; 95%CI: 3.8%-43.4%).

Conclusion: DGA cream may be safe and effective in the prophylaxis of HFSR in mRCC patients who receive sunitinib therapy (Trial ID: jRCTs051180051).

Key words: hand-foot skin reaction; sunitinib; multiple tyrosine kinase inhibitor; ascorbic acid; DGA.

Lessons Learned

- This clinical trial demonstrated that 1% bis-glyceryl ascorbate-containing cream (DGA cream) was safe and effective for the prevention of hand-foot skin reaction (HFSR) in patients with metastatic renal cell carcinoma.
- Confirmatory evaluation with a sufficiently long period of investigation is necessary for determining associations between the intensive management of HFSR and favorable prognosis for multiple tyrosine kinase inhibitor therapy.

Discussion

This phase I/II study demonstrated the safety and effectiveness of the 1% bis-glyceryl ascorbate (Amitose DGA, Seiwa Kasei, Osaka, Japan)-containing cream (DGA cream) for sunitinib-induced HFSR in patients with MRCC. In phase I, no dermatological abnormalities were induced by DGA cream. DGA is a commercial cosmetic preparation; therefore, the safety of this product is already tested and fundamentally high. In phase II, the incidence of HFSR in patients of the FAS was significantly lower than the previously-reported

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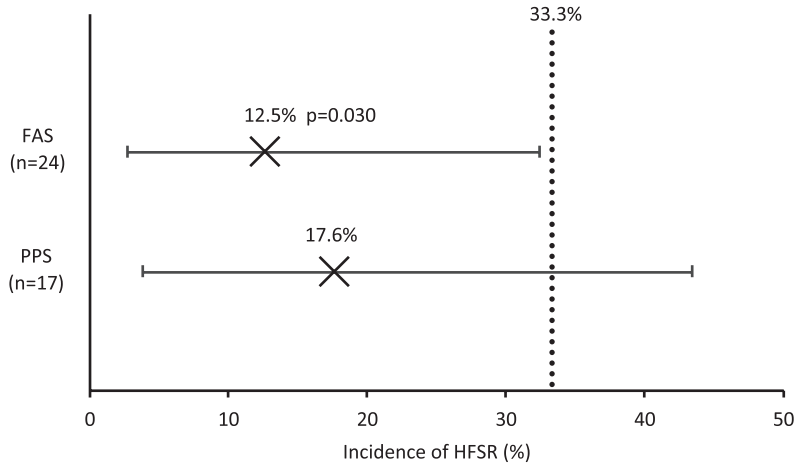

Figure 1. Incidence rates of HFSR. Cross markers indicate the rate of HFSR incidence. Horizontal bars indicate 95% confidential intervals. The dotted line indicates the threshold ratio of HFSR incidence in this study (33.3%). Abbreviations: HFSR, hand-foot skin reaction; FAS, full analysis set; PPS, per protocol set.

incidence rate of sunitinib-induced HFSR (Fig. 1). The pharmaceutical efficacy of DGA cream was not established because the CI of the incidence rate in the PPS crossed the threshold determined from the previously-reported incidence rate. Five of the 7 patients, who discontinued DGA cream within 6 weeks, discontinued sunitinib therapy due to disease progression at the median time of progression-free survival or at a shorter interval. In fact, patients in the PPS excluding them had a longer progression-free treatment time. It is possible that they are more likely to develop HFSR due to the association between HFSR incidence and the therapeutic efficacy of TKI therapy. Females have been reported to be at a higher risk for the development of HFSR. Two of the three study participants who developed HFSR were females (67%). The proportion of female participants was 45.8%—greater than 17.4%-26.5% proportion in other Japanese clinical studies for the same-scheduled sunitinib therapy. The median total plasma sunitinib concentration in patients with available data was higher than the reported values in patients with adverse events, including HFSR. Therefore, our study included a population with higher risk for HFSR development. All 3 patients who developed HFSR during the treatment period discontinued sunitinib therapy due to severe adverse events, including HFSR. Our participants had similar progression-free survival and time to treatment failure as in previous Japanese and Asian reports. The study's DGA cream treatment period (6 weeks) was too short to evaluate associations between the intensive management of HFSR and favorable prognosis for sunitinib therapy. Although the data presented here are preliminary, they provide valuable evidence to support the use of DGA cream for the prevention of HFSR.

Trial Information	
Disease	renal cell carcinoma—clear cell
Stage of disease/treatment	metastatic/advanced
Prior therapy	no designated number of regimens
Type of study	phase I/II, single arm
Primary endpoint	safety and efficacy
Investigator's Assessment	active but statistical power is low

Additional Details of Endpoints or Study Design

Study Design

This study was a phase I/II, single-center, uncontrolled, single-arm, open-label clinical trial to evaluate the safety and efficacy of bis-glyceryl ascorbate (Amitose DGA)-containing cream (DGA cream) as a prophylaxis for sunitinib-induced hand-foot skin reaction (HFSR).

Inclusion and Exclusion Criteria

We included individuals capable of providing informed consent, aged 20 years or older, with histologically diagnosed metastatic renal cell carcinoma (mRCC), receiving sunitinib therapy, with or without prior molecular targeted therapy and before or after nephrectomy. All patients had an Eastern Cooperative Oncology Group Performance Status of 0-2 and were expected to survive for more than 12 weeks at screening. Finally, all the included patients were determined to exhibit higher compliance for applying the investigational cream, attending clinical visits, undergoing laboratory tests, and keeping a personal diary based on the study protocol. We excluded patients with dermatological abnormalities of the palmar or plantar surfaces; those who used topical medications on the palmar or plantar surfaces, except for heparinoid or urea-containing cream; those who were unable to apply the heparinoid or urea-containing cream to the palmar or plantar surfaces; those with grade 1 or higher HFSR based on Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0; and those with active infections requiring treatment, at the start of sunitinib therapy. We also excluded patients with severe liver injury (ie, alanine aminotransferase ≧5 ×

upper limit of normal or 2 × individual baseline value), severe kidney injury (ie, serum creatinine level ≧2 × individual baseline value), and other patients who were determined to be inappropriate for study participation by the investigator.

Intervention

The participants applied three finger-tip units of DGA cream all over both the palmar and plantar surfaces more than three times a day, within two treatment cycles (6 weeks) of sunitinib. They also applied heparinoid or urea-containing cream as a standard preventive care for HFSR following application of the investigational cream. The participants were instructed to apply the investigational cream to skin, such as when washing their hands or feet, during face washing, or after bathing. The participants kept a personal diary to record the number of applications of DGA cream.

Primary Outcomes

The primary outcome of phase I was dermatological abnormalities on the palmar or plantar surfaces within 2 cycles (6 weeks) of sunitinib therapy. The primary outcome of phase II was development of grade 1 or higher HFSR within 6 weeks after the initiation of sunitinib therapy.

Secondary Outcomes

The secondary outcomes of phase I were hematological test abnormalities within the observation period. The secondary outcomes of phase II were development of grade 2 or higher HFSR within 6 weeks of sunitinib therapy, progression-free survival and time to treatment failure of sunitinib therapy, dermatological abnormalities of the palmar or plantar surfaces within the observation period, and development of grade 2 or higher HFSR within 3 weeks after completion of the investigational treatment.

Assessments

Dermatological Abnormalities

Dermatological abnormalities were defined as pruritus, dryness, purpura, maculopapular erythema, bulla/vesicle formation, erythroderma, hyperpigmentation, and hypopigmentation.

Hand-Foot Skin Reaction

Hand-foot skin reaction grading were done according to that for palmar-plantar erythrodysesthesia syndrome, as described by the National Cancer Institute CTCAE, version 4.0. Both the dermatologist and the urologist determined the efficacy of the investigational preparation. Hand-foot skin reaction was constantly checked by the hospital urologist during the first 2 weeks of sunitinib therapy; during this period, the patient remained in-hospital. During week 3 and 6 outpatient clinical visits, participants received dermatological examinations by a dermatologist. This examination focused on dermatological abnormalities of the palmar or plantar surfaces to assess the safety of the DGA cream in phase I. The dermatologist additionally assessed the efficacy of the DGA cream at these visits during phases I and II.

Compliance for Use of Investigational Preparation

Participant compliance was monitored by the medical staff while the participants were inpatients. Once participants were transitioned to outpatient treatment, we calculated a compliance ratio for the investigational preparation by determining instances of daily use, based on diaries kept by individual participants.

Plasma Concentration of Sunitinib

Plasma concentrations of sunitinib were measured 10-14 days after the start of sunitinib therapy, as per usual care practice; the trough level of total concentration of sunitinib and its metabolite *N*-desethyl-sunitinib were measured.

Progression to Sunitinib Therapy

Before the introduction of sunitinib, all patients received radiological examinations, including computed tomography imaging of the brain, chest, and abdomen, or radionuclide bone scans, or both. All responses were assessed by a treating physician based on the Response Evaluation Criteria in Solid Tumors version 1.1.

Discontinuation of Study Subjects

Use of DGA cream was permanently discontinued for the following cases, if their consent was withdrawn; if participants declined to comply with procedures of this study; if inadequacies were found after enrollment; if sunitinib therapy was determined to be unnecessary because of mRCC resolution; if the patient was unable to continue sunitinib therapy because of disease progression, complications, or adverse events induced by sunitinib; or if other issued emerge that warrant study discontinuation, according to the investigator.

Statistical Methods

Sample Size Calculation

The sample size for the phase I study was primarily based on the extent of necessity and concernment. To limit the potency of intolerable adverse events, the investigational preparation was an ascorbic acid derivative, which is generally equivalent to cosmetic preparations; however, there were no practical safety data pertaining to the administration of DGA cream to patients with mRCC receiving sunitinib therapy. In this study, the safety of DGA was confirmed by a cohort that integrated 5 patients.

The sample size for the phase II study was 30 participants, in combination with the phase I study sample (ie, five phase I participants and 25 additional participants). In previous reports from our institution, HFSR of any grade was 33.3%; HFSR of grade 3 was 2.2% among patients with mRCC who were treated with a 2-week-on and 1-week-off sunitinib schedule. Given that the investigational preparation can prevent up to 75% of grade 1-2 HFSR, we estimated that the frequency of HFSR of any grade among patients using the investigational preparation is 10%. In the case of this study, 25 participants were needed to guarantee an α of 0.05 and 80% statistical power, with no continuity correction.

Primary Analysis

In the phase I study, if 2 or more participants out of 5 (≥40%) show dose-limiting toxicities defined as grade 2 or higher dermatological abnormalities during the safety evaluation period, phase I enrollment was supposed to stop. The null hypothesis of the phase II study was defined as the frequency of development of HFSR of any grade was 33.3%, and the frequency of development of HFSR of any grade in

one-sample was analyzed with a significance level of 5%. Primary analysis in phase II was performed by intention-to-treat analysis on the full analysis set (FAS) defined as the population including all participants who used DGA cream once in the study duration.

Secondary Analysis

Secondary analyses considered per-protocol set, including participants who completed the treatment according to the scheduled protocol. Multiplicity was not adjusted in this analysis. Hypothesis testing was performed with a two-sided 5% significance level and a two-sided 95% confidence interval (CI).

Progression-free survival and time to treatment failure were determined using the Kaplan-Meier method estimate; medians and 95% CIs were calculated.

Investigator's Analysis

Active but statistical power is low

Drug Information	
Bis-glyceryl ascorbate (Amitose DGA)-containing cream	
Generic/working name	Bis-glyceryl ascorbate (Amitose DGA)-containing cream
Drug type	Topical ascorbic acid derivative
Route	Topical application
Schedule of administration	The participants applied three finger-tip units of DGA cream all over both the palmar and plantar surfaces more than three times a day, within two treatment cycles (6 weeks) of sunitinib. They also applied heparinoid or urea-containing cream as a standard preventive care for HFSR following application of the investigational cream.

Patient Characteristics	
Number of patients, male	13
Number of patients, female	11
Stage	
Age	Median (range): 61 (30-74) years
Performance Status: ECOG	0—15 1—7 2—2 3—0 Unknown—0
Other	Body weight, median (range), kg: 60.0 (39.3-87.1). First-line mRCC therapy by sunitinib, *n*(%): 20 (83.3%)

Primary Assessment Method: Phase I	
Title	**Dermatological abnormalities**
Number of patients screened	5
Number of patients enrolled	5
Number of patients evaluable for toxicity	5
Number of patients evaluated for efficacy	0
Evaluation method	Diagnosis by dermatologist

Outcome Notes

Dermatological abnormalities were defined as pruritus, dryness, purpura, maculopapular erythema, bulla/vesicle formation, erythroderma, hyperpigmentation, and hypopigmentation.

Results

No dermatological abnormalities occurred in the first 5 patients enrolled in the phase I study.

Primary Assessment Method: Phase II	
Title	**HFSR**
Number of patients screened	26
Number of patients enrolled	25
Number of patients evaluable for toxicity	24
Number of patients evaluated for efficacy	24
Evaluation method	National Cancer Institute CTCAE, version 4.0
Response assessment OTHER	*n* = 3 (12.5%)

Outcome Notes

Development of grade 1 or higher HFSR according to that for palmar-plantar erythrodysesthesia syndrome, as described by the National Cancer Institute CTCAE, version 4.0.

Results

Grade 0: *n* = 21 (87.5%)
Any grade HFSR: *n* = 3 (12.5%)
Grade 1: *n* = 2 (8.3%)
Grade 2: *n* = 1 (4.2%)

Secondary Assessment Method: Phase II	
Title	**Therapeutic efficacy of sunitinib**
Number of patients screened	26
Number of patients enrolled	25
Number of patients evaluable for toxicity	24
Number of patients evaluated for efficacy	24
Evaluation method	RECIST 1.1
(Median) duration assessments PFS	402 days, CI: 240-564
(Median) duration assessments duration of treatment	272 days, CI: 50-494

Assessment, Analysis, and Discussion	
Completion	did not fully accrue
Investigator's Assessment	active but statistical power is low

Hand-foot skin reaction is not a life-threatening side effect but can drastically decrease quality of life and adherence to chemotherapy. The reported incidences of grade 3 HFSR induced by multiple tyrosine kinase inhibitors (TKIs) are 8% and 17% in patients taking sorafenib and cabozantinib, respectively.[1] Traditional prophylaxes do not have sufficient efficacy. Some novel prophylactic compounds have been studied; however, no products have established evidence for efficacy in preventing HFSR, except for urea-containing topical preparations.[2]

Bis-glyceryl ascorbate is a novel ascorbic acid derivative with improved cutaneous permeability and stability on the skin epidermis and in keratinocytes. The investigational product in this study was a cream containing 1% bis-glyceryl ascorbate (Amitose DGA, Seiwa Kasei, Osaka, Japan). Our pharmaceutical tests to evaluate permeability and stability indicated that 1% was the maximum concentration to show increased permeability to healthy human skin; stability was similar in the various concentrations examined. Our in vitro preliminary study indicated that 1% is the maximum concentration for any detectable increase in the protective effects of Amitose DGA on cell growth inhibition by sunitinib; higher concentrations did not cause a significant increase in permeability or protective effects. The safety of Amitose DGA containing cream (DGA cream) was examined in 10 healthy adult volunteers prior to this study. No skin irritation at 1 hour and 24 hours after application of DGA cream was found in any volunteer.

In the phase I study, no dermatological abnormalities were induced by the intervention (Table 1). The safety of DGA cream in patients with mRCC was at a high level, similar to that in healthy volunteers. DGA cream is a cosmetic; therefore, its safety is already tested and fundamentally high. Our study detected some hematological abnormalities; however, these adverse events were mainly due to the sunitinib therapy itself (data not shown).

In the phase II study, the incidence of HFSR in participants of the FAS was significantly lower than the threshold rate for sunitinib-induced HFSR (Fig. 1), demonstrating the effectiveness of DGA cream in mRCC patients. The rate predefined as a threshold (33.3%) is the reported HFSR incidence rate indicated by the same-scheduled sunitinib therapy at our hospital.[3] Previous reports showed a 58% incidence rate of HFSR, induced by sunitinib at a 2 week on/1 week off schedule, within the first three cycles in Japanese patients.[4] The HFSR rate within the overall therapeutic duration in Chinese patients was reported to be 46.9%.[5] Thus, our predefined threshold is considered a slightly stricter value in conditions with standard precautions for HFSR, although our evaluation period for HFSR was 6 weeks after sunitinib therapy. The pharmaceutical efficacy of DGA cream was not established because the CI of the incidence rate in the per protocol set (PPS), obtained from only 17 participants (Fig. 2), crossed the predefined threshold determined from the previously-reported incidence rate (Fig. 1). Five of the 7 patients, who discontinued DGA cream within 6 weeks, discontinued sunitinib therapy due to disease progression at the median time of progression-free survival or shorter one. In fact, patients in the PPS excluding them had a longer progression-free treatment time (Fig. 3A). There is a possibility that the participants selected for the PPS had a better prognosis for sunitinib therapy; they may represent a population more likely to develop HFSR, due to the association between the incidence of HFSR and the therapeutic efficacy of TKIs.[6] Females are at a higher risk for developing HFSR.[7] The proportion of females in this study was 45.8% (Table 2), which was greater than that of other Japanese clinical studies (17.4%-26.5%) for the same or similar schedule of sunitinib therapy.[3,4,7,8] Thus, our study included a population with a higher risk for HFSR development. All 3 patients who developed HFSR during the study period discontinued sunitinib therapy due to severe adverse events, including HFSR.

The median total sunitinib (sunitinib plus an active metabolite *N*-desethyl sunitinib) plasma concentrations in patients with available data were 106 and 102 ng/mL in the FAS and in PPS sets, respectively (Table 2). Drug concentrations in some patients were not measured, as measurements were performed in clinical care, not in the study protocol. A total

sunitinib plasma concentration of 50-100 ng/mL is suggested for favorable prognosis.[9,10] The trough total sunitinib concentration in Japanese mRCC patients has been reported as 91.8 ng/mL.[9] Another study reported median total sunitinib plasma concentration in patients who discontinued sunitinib therapy as 92.7 ng/mL.[11] It has been reported that patients who develop HFSR have slightly higher total sunitinib concentrations than those who do not (75.2 ng/mL vs 64.2 ng/mL).[12] Our participants had higher total sunitinib concentrations and a consequently higher risk of adverse events, including HFSR, than previous study participants.

The median progression-free survival (PFS) and the time to treatment failure (TTF) in this study were 402 days (95% CI: 240-564 days) and 272 days (95%CI: 50-494 days), respectively (Fig. 3B and C). The PFS for sunitinib therapy was reported as 11.2 months (340 days) in Chinese mRCC patients with a dosing schedule of 2 weeks on/1 week off, and 12.2 months (371 days) in Japanese mRCC patients with a traditional dosing schedule of 4 weeks on/2 weeks off.[5,13] Our study participants had PFS similar to these reports. The management of adverse events induced by multiple TKIs is associated with a prolonged treatment period.[1] In our study, the effects of DGA cream on PFS and TTF could not be fully evaluated because the duration of DGA cream use (6 weeks) was much shorter than the duration of sunitinib therapy. Further clinical studies are necessary to evaluate whether DGA cream affects therapeutic outcomes with multiple TKIs.

This preliminary study had some limitations. We chose a small scale, single-arm, open-label design in order to maximize subject exposure and increase the likelihood of achieving the study endpoints. Our study terminated before completion because of decline of sunitinib therapy; therefore, statistical power was 62%, and it was insufficient to emphasize the effect of intervention. We evaluated the effects of combination therapy involving DGA cream and a moisturizing agent, as in existing standard-of-care prophylaxis, such as urea- or heparinoid-containing cream, considering the evidence of prior in vitro study. The efficacy of DGA cream itself on HFSR was not evaluated. The results in the PPS cannot be generalized to a wider population because of the small number of participants in our study protocol.

This phase I/II study demonstrated the safety and effectiveness of DGA cream for sunitinib-induced HFSR in mRCC patients. The data presented here provide preliminary but valuable evidence to support the use of DGA cream for the prevention of HFSR. DGA cream may abate pain and suffering in patients, and enhance therapeutic outcomes in multiple TKI therapy. This study also indicates a high potential for cosmetic product use to overcome serious medical issues.

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Conflict of Interest

Kazuhiro Yamamoto: Momotani Juntenkan Ltd. (research funding). The other authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

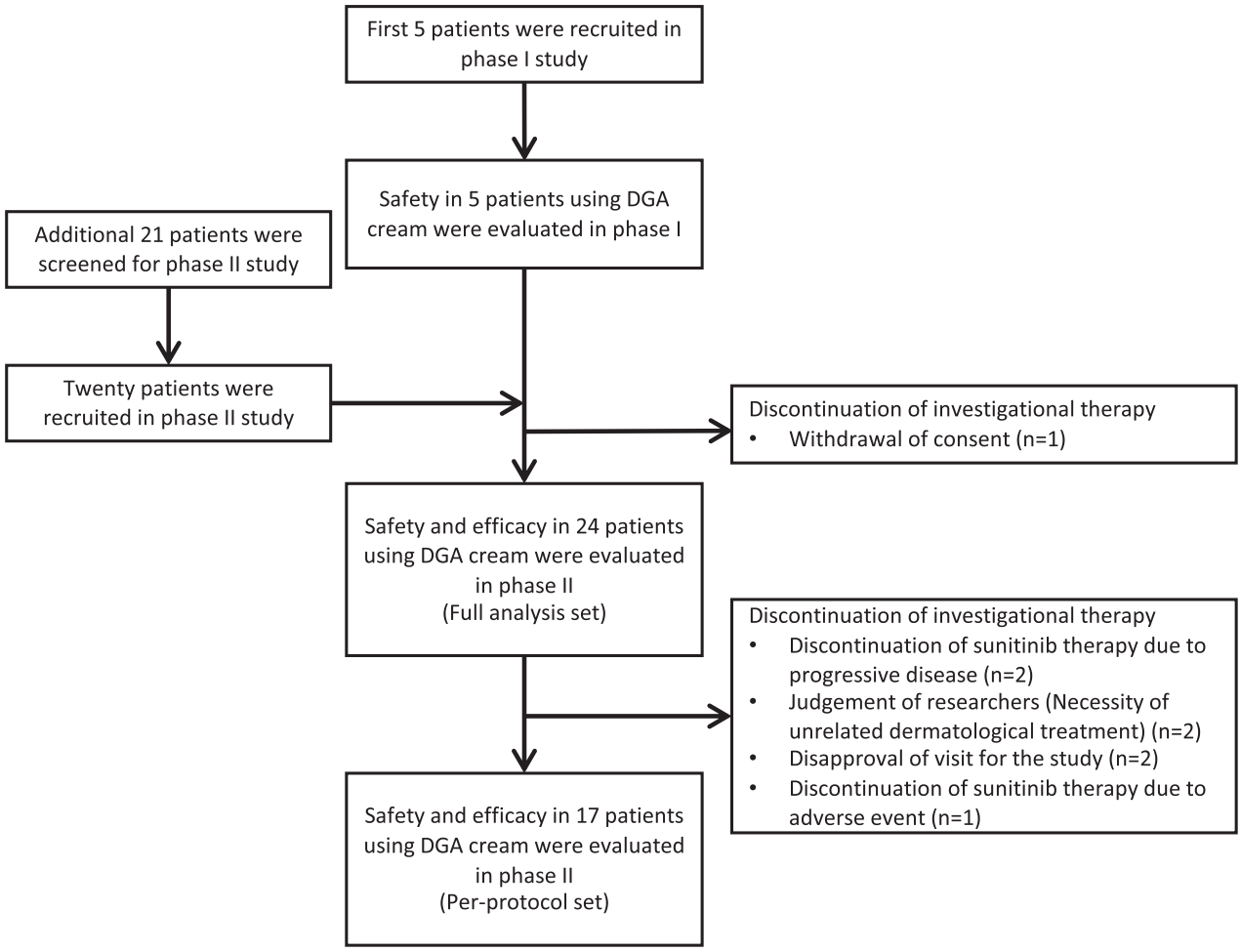

Figure 2. Participant flowchart. Abbreviation: DGA cream, 1% bis-glyceryl ascorbate (Amitose DGA) containing cream.

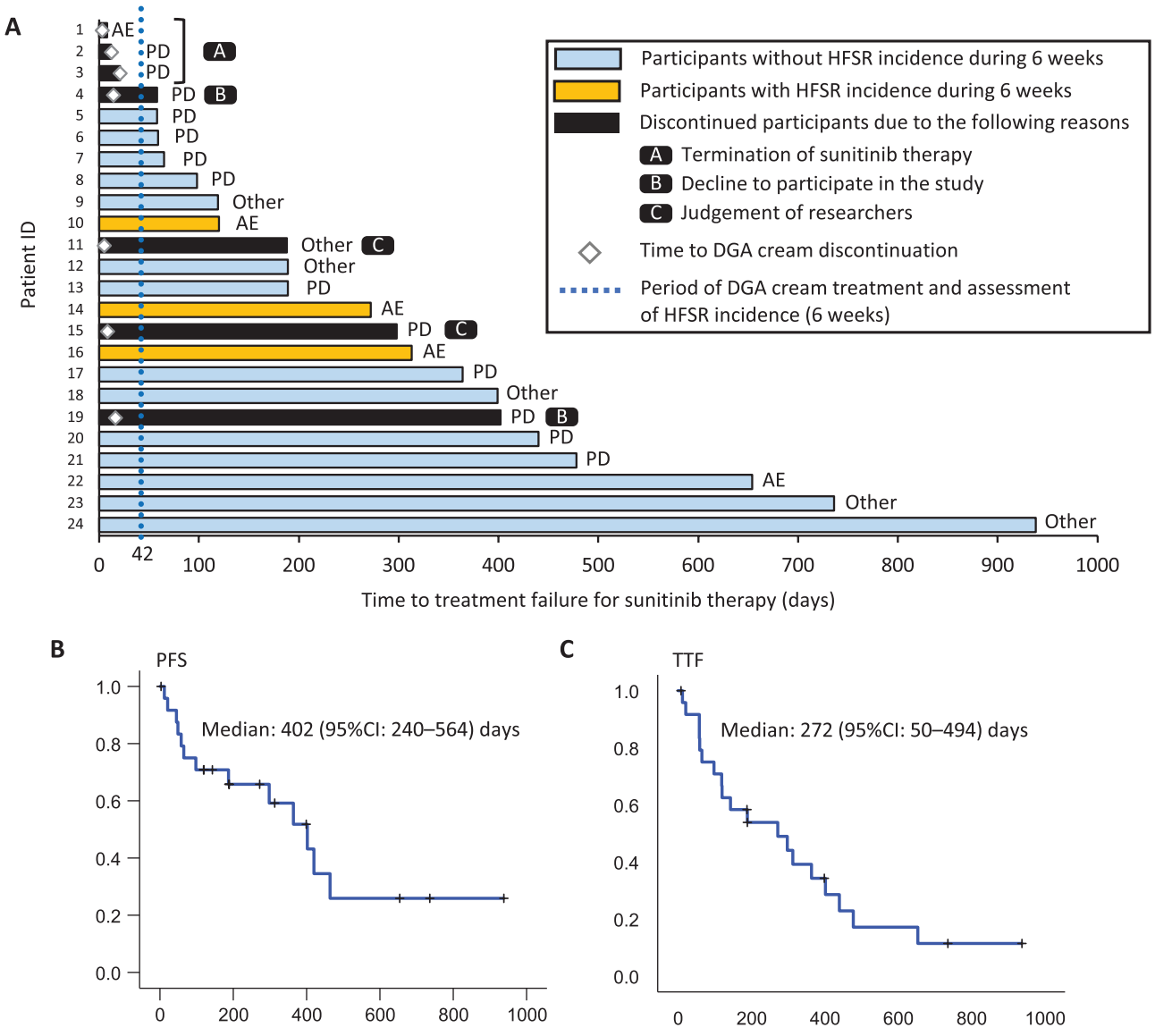

Figure 3. Time to event analysis and reasons for sunitinib discontinuation. DGA cream was applied for 6 weeks; HFSR development was evaluated during this period. (**A**) TTF of sunitinib therapy for each participant. The bar indicates the TTF for sunitinib therapy. Each black bar indicates a discontinuation of DGA cream use, the reasons indicated by black squares. Each open rhomboid shows the time to discontinuation during the study period. Each orange bar indicates an incidence of HFSR during the observation period. The text at end of the bar indicates the reason for discontinuation of sunitinib therapy. The dotted line indicates the period of DGA cream treatment and assessment of HFSR. (**B**): Kaplan-Meier curve of PFS. (**C**) Kaplan-Meier curve of TTF. Abbreviations: HFSR, hand-foot skin reaction; TTF, time to treatment failure; ID, identification; PPS, per protocol set; AE, adverse event; PD, progressive disease; PFS, progression-free survival; CI, confidence interval.

Table 1. Safety assessment in the participants enrolled in phase I study.

		N (%)
Cutaneous abnormalities	Pruritus	0/5 (0)
	Dryness	0/5 (0)
	Purpura	0/5 (0)
	Maculopapular erythema	0/5 (0)
	Bulla/vesicle formation	0/5 (0)
	Erythroderma	0/5 (0)
Cutaneous melanocytic abnormalities	Hyperpigmentation	0/5 (0)
	Hypopigmentation	0/5 (0)

Table 2. Demographic and clinical characteristics of full analysis set and per protocol set participants.

	FAS	PPS
n	24	17
Female, *n* (%)	11 (45.8)	8 (47.1)
Age, median (range), years	61 (30-74)	61 (30-74)
Body weight, median (range), kg	60.0 (39.3-87.1)	58.8 (39.3-74.0)
ECOG-PS, *n* (%)		
0	15 (62.5)	10 (58.8)
1	7 (29.2)	5 (29.4)
2	2 (8.3)	2 (11.8)
Sunitinib initial dose, *n* (%)		
25 mg/day	4 (16.7%)	4 (23.5)
37.5 mg/day	19 (79.2%)	12 (70.6)
50 mg/day	1 (4.2%)	1 (5.9%)
First-line mRCC therapy by sunitinib	20 (83.3%)	13 (76.5%)
Total sunitinib plasma concentration, median (range), ng/mL	106 (70.4-172)[a]	102 (70.4-172)[b]

[a]Number of the patients with available data was 11.
[b]Number of the patients with available data was 8.